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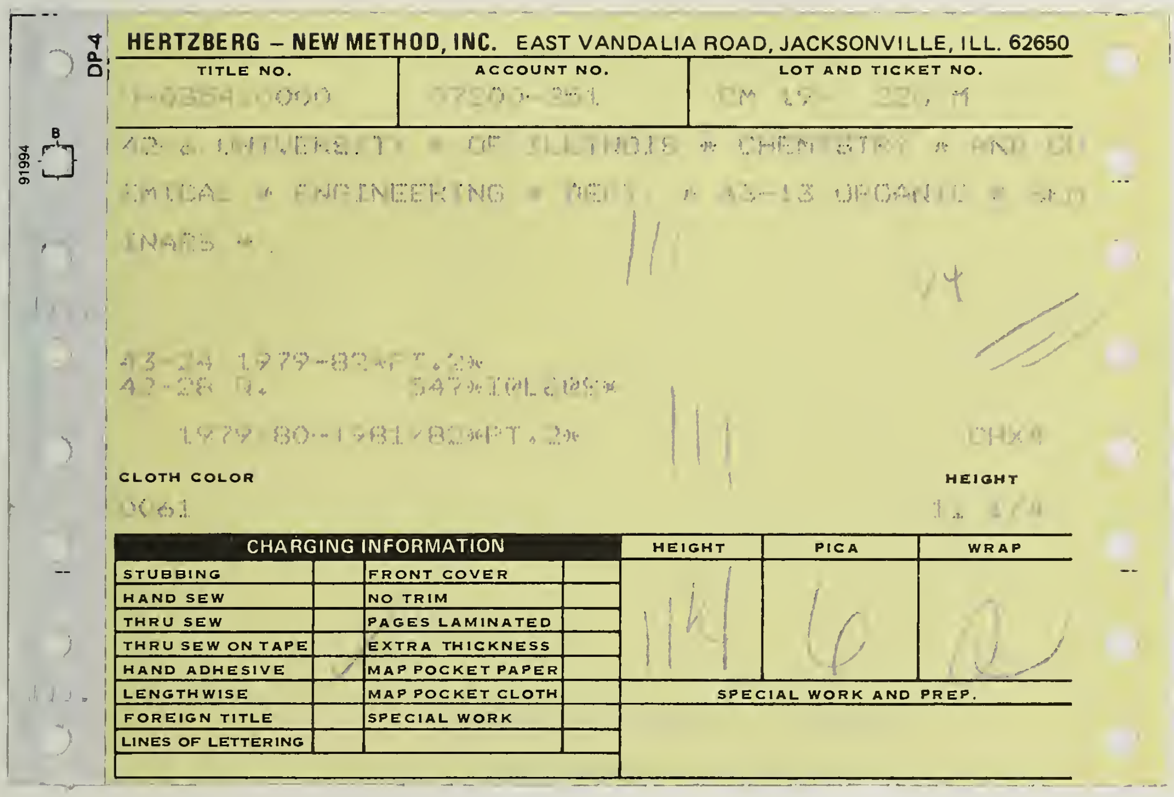
ORGANIC SEMINAR ABSTRACTS



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ORGANIC SEMINAR ABSTRACTS

1979-80, Semester II

University of Illinois

School of Chemical Sciences
Department of Chemistry
University of Illinois
Urbana, Illinois
61801

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II Semester, 1979-80

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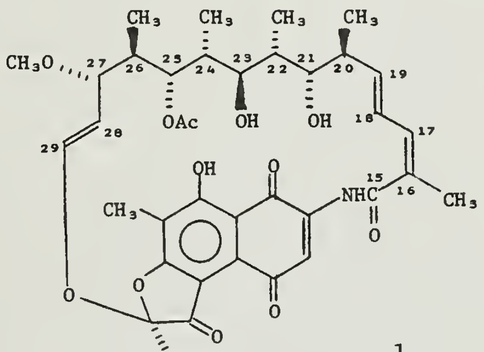
SOME RECENT ADVANCES IN THE CONTROL OF STEREOCHEMISTRY IN ACYCLIC SYSTEMS

Reported by David W. Robertson January 28, 1980

Nature continues to provide a plethora of molecules which, for aesthetic, economic, and medicinal reasons, captures the attentions of synthetic organic chemists. Recently, efforts in many laboratories have focused on targets in the ansamycin,[1a] polyether,[1b] and macrolide[1c] antibiotic families; these polyoxygenated molecules are rich in asymmetry and represent a formidable synthetic challenge to the imaginations and current methodologies of chemists. Many of these compounds have acyclic or macrocyclic structures which render them conformationally mobile. While stereochemical control can be routinely achieved in the synthesis of conformationally immobile systems, stereochemical control in synthetic manipulations involving conformationally flexible molecules remains one of the unsolved problems in organic chemistry. The traditional strategy in synthesizing molecules such as these has involved controlling the stereochemistry by using conformationally unambiguous 5- or 6-membered ring system precursors which can be ultimately opened and incorporated into acyclic or macrocyclic targets. The recent independent syntheses of the Prelog-Djerassi lactone by Stork[2] and White[3] and the macrolide syntheses by Masamune[1c] and Corey[4] attest to the power of such an approach. Much interest has been stimulated, however, in the control of stereochemistry in conformationally heterogeneous, acyclic systems. Many investigators have now begun to penetrate this largely unexplored region of organic synthesis and several novel solutions have been advanced. Some of these solutions will be discussed.

As is exemplified by carbons 19-27 of the ansa bridge unit of rifamycin (1), many of the antibiotic moities, in principle at least, can be synthesized by a series of aldol-like condensations if sufficient stereochemical control can be incorporated into each condensation. The effects of steric bulk, solvent, nature of the metal, kinetic versus thermodynamic control, and the geometry of the enolate on the stereochemical outcome of the aldol condensation have been investigated. Early work by House[5] demonstrated that in aldol condensations where two new stereocenters are generated, _threo_ aldols can be selectively synthesized using preformed enolates in the presence of Zn^{2+}. More recently Heathcock[6,7] and co-workers have found that, under the proper conditions, complete kinetic[8] stereoselection can be achieved,[6a] with the (Z)-enolate giving the _erythro_ aldol exclusively (Eq. 1) and the (E)-enolate affording the _threo_ aldol exclusively (Eq. 2) if R is sufficiently



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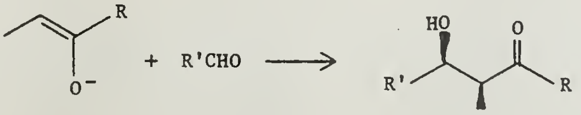

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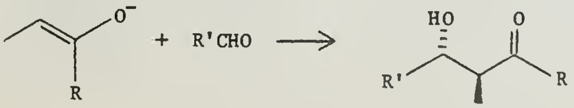
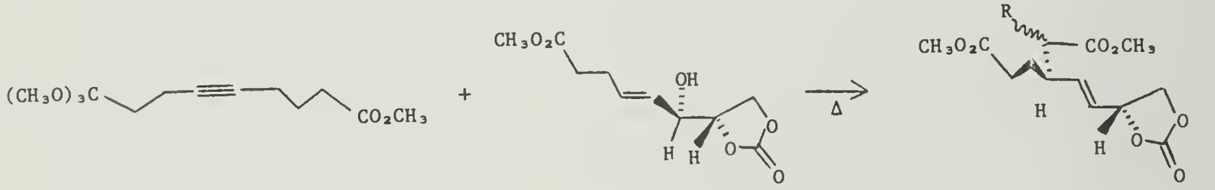


(2)

bulky. If the aldehyde contains a chiral center adjacent to the carbonyl, then Cram's rule[9] and the enolate geometry can be used to predict the stereochemical relationship of the three contiguous chiral centers produced in the reaction. Chan et al.[10] have found that the (E)-isomer of O-ethyl-O-trimethylsilylmethylketene acetal reacts in the titanium tetrachloride promoted cross-aldol condensation to give threo products; surprisingly, the (Z)-isomer reacts nonstereospecifically. Evans[11] and Masamune[12] have also investigated stereoregulated varients of the aldol condensation, with their studies focusing on the use of geometrically defined boron enolates. The use of boron enolates appears to be more general and more diastereoselective than the use of lithium[11a] or aluminum[11a,13] enolates. Meyers[14] has reported that internally chelated lithium ester enolates can lead to threo-2-alkyl-3-hydroxy acids. Most, if not all, of the results obtained to date in the stereoregulated aldol-like condensations are explainable in terms of a cyclic, 6-center transition state, analogous to that of a pericyclic process and evidence continues to accumulate indicating the aldol condensation is a pericyclic process.[6a,15]

Claisen and Cope rearrangements have seen long and continued use in natural products synthesis because they lead to predictable olefin geometries.[16] In addition, the stereochemistry at chiral centers in acyclic systems can be controlled by [3,3] sigmatropic rearrangements through intramolecular transfer of asymmetry.[17,18] In Stork's ingenious chiral prostaglandin synthesis[19] two Claisen rearrangements were used, with the first controlling the stereochemistry of an olefin, and the second transferring chirality stereospecifically from a carbon-oxygen bond to a newly formed carbon-carbon bond (Eq. 3). In a series of publications[20] on the synthesis of optically active α-tocopherol, Hoffman-LaRoche workers have shown that saturated, acyclic isoprenoids such as 2, a structural unit found in many natural products, can be produced in optically active form by a series of stereospecific [3,3] sigmatropic rearrangements. Claisen rearrangements can also be used to stereoselectively synthesize aldol-like products.[18d]



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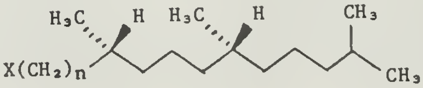

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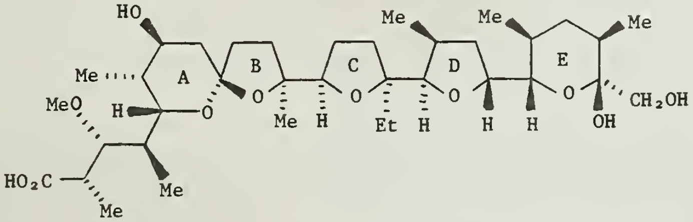
The epoxidation of cyclic allylic alcohols with organic peroxyacids or hydroperoxides catalyzed by transition metals often proceeds with excellent stereoselectivity.[21] Several groups have extended these results to acyclic systems and found that allylic, homoallylic, and even bishomoallylic alcohols can be stereoselectively epoxidized.[22] Stereoselective formation of halohydrins by several novel methods has also been explored as a route to stereochemically pure epoxides.[23]

Numerous other methods for diastereoselective synthesis in acyclic systems have appeared in the literature. The additions of allyl boronates[24] and allyl chromium species[6c] to aldehydes proceed with excellent diastereoselectivity. Trost has shown that a transition metal complex can be used as a template to relay stereochemical information from a ring to an acyclic system,[25] and Isobe has demonstrated that heteroconjugate additions in an acyclic system can lead to complete asymmetric induction.[26]

Kishi's synthesis of the polyether antibiotic monensin (3),[27] perhaps the most elegant total synthesis yet achieved,[28] is a manifestation of the great synthetic power available through the use of methods for stereocontrol in acyclic systems developed in the past several years. The development of these methods and the promise of more herald a new era for synthetic organic chemistry.



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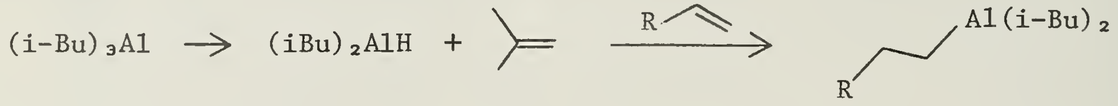
TRANSITION METAL CATALYZED HYDROALUMINATION OF OLEFINS AND ACETYLENES

Reported by Ralph Lessor February 18, 1980

Organoaluminum compounds have been known for about one hundred years, but have received little attention as synthetic intermediates.[1] Difficulty of preparation and a lack of varied uses for the organoaluminum compounds have combined to direct the attention of organic chemists toward more promising organometallics. Recent discoveries relating to the combination of aluminum hydrides with transition metals, most notably titanium and zirconium, have made organoaluminum compounds easier to prepare, and as a result, the previously limited synthetic utility of such compounds is expanding rapidly.

Historically, trialkylaluminums and organoaluminates have been prepared by reaction of other organometallics with aluminum halides, by reaction of organic halides with aluminum metal, or by reduction of organoaluminum halides. Direct preparation from olefins has been limited to high-pressure and high-temperature reaction of olefins with lithium aluminum hydride, or high-pressure hydroalumination using hydrogen gas and aluminum metal. While of great utility as industrial processes, these reactions are of little or no use in a laboratory synthesis. Olefin exchange reactions with commercially available organoaluminums have been used to prepare some compounds, but the necessity of removing the original olefin (usually isobutene) from a complex mixture of organoaluminums severely limits the synthetic utility of such processes. This reaction proceeds by elimination of olefin to give an organoaluminum hydride, which then adds across the double bond of another olefin in an anti-Markownikoff manner, i.e., the aluminum becomes bonded to the less substituted olefinic carbon (Eq. 1). Since addition proceeds in the same sense as the well-known hydroboration reaction, the use of hydroalumination reactions for the modification of olefins has received little attention, despite the high selectivity of hydroalumination for terminal olefins.



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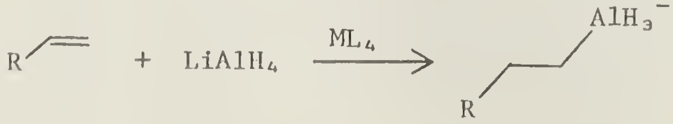
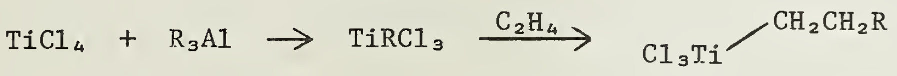
In 1976 it was discovered by the groups of Sato and Isagawa that titanium tetrachloride and titanocene dichloride effectively catalyzed the addition of lithium aluminum hydride across double bonds.[2-4] The catalyzed reaction proceeds with the same regioselectivity as the uncatalyzed reaction, but under milder conditions and with less chance of olefin isomerization. Shortly thereafter it was discovered that zirconium tetrachloride and zirconocene dichloride (Cp_2ZrCl_2) are also effective catalysts for this reaction, and that vanadium tetrachloride is less effective[3,5] (Eq. 2).



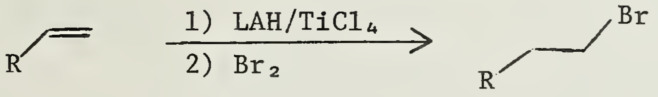
L = Cl, C_5H_5 M = Zr, Ti (2)

The use of aluminum compounds in conjunction with transition metals is not without precedent. Various mixtures of aluminum alkyls and transition metal halides catalyze the polymerization of olefins in a process known as Ziegler-Natta polymerization. The mechanism of this reaction, which is undoubtedly related to that of catalyzed hydroalumination, is believed to involve the formation of an organotransition metal compound, complexation of the olefin, and insertion of the olefin into the carbon-transition metal bond (Eq. 3). It has been shown that aluminum is not essential for catalysis, since it can be replaced by organometallic compounds of other electropositive metals such as lithium, magnesium, zinc, or beryllium.[6]



$$TiCl_4 + R_3Al \rightarrow TiRCl_3 \xrightarrow{C_2H_4} Cl_3Ti{-}CH_2CH_2R \qquad (3)$$

When a terminal olefin reacts with an excess of lithium aluminum hydride in the presence of one of the transition metal catalysts, hydroalumination proceeds in high yield at room temperature, or slightly above, to give the anti-Markownikoff organoaluminate. Terminal olefins react far more rapidly than do internal or cyclic olefins, thus allowing selective reaction.[2,3] The high regioselectivity of this reaction has been demonstrated by halogenolysis of the organoaluminates to give 1-haloalkanes in high yields, with only a trace of 2-haloalkanes (Eq. 4). The same regioselectivity, observed in the uncatalyzed hydroalumination reaction, has generally been attributed to steric effects either in a four-center transition state or in a proposed π-complexed intermediate formed prior to hydroalumination.[7] The dominance of steric effects over electronic effects is suggested by the observed change in regioselectivity for the reactions of 1-phenylpropyne[7b] and t-butylphenylacetylene[7a] with di-isobutyl aluminum hydride (Scheme I). The regioselectivity of hydrozirconation is also anti-Markownikoff, and has simlarly been attributed to steric effects.



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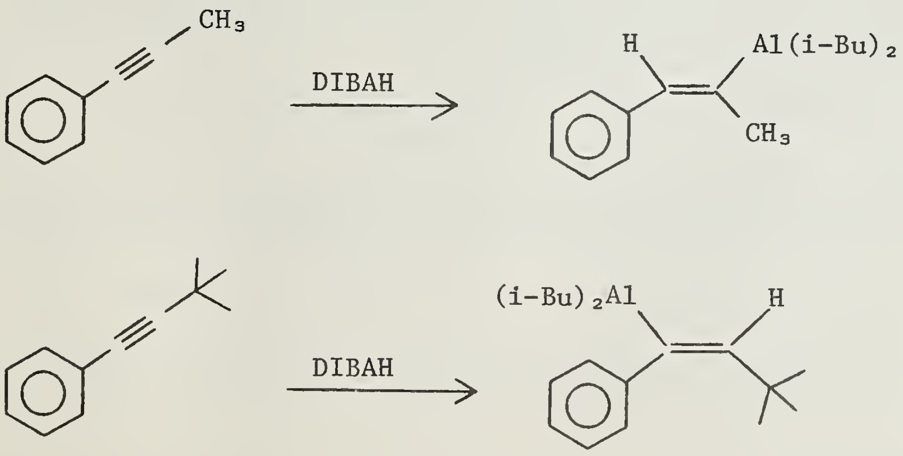
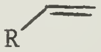
Scheme I



The catalyzed hydroalumination of olefins is believed to occur in an overall cis manner via a four-center pericyclic process, but the stereochemistry of the catalyzed reaction with olefins has not been conclusively demonstrated. In the case of transition metal catalyzed hydroalumination or carboalumination of acetylenes, the organoaluminum intermediates have been shown by NMR spectroscopy and analysis of hydrolysis products to be formed by cis addition across the triple bond to give an alkenylaluminum species.[8]

Scheme II

$$2\,\mathrm{LAH} + Cp_2ZrCl_2 \longrightarrow Cp_2Zr(AlH_3)_2 + \tfrac{1}{2}H_2 + 2\,LiCl$$

$Cp_2Zr(AlH_3)_2$ +  $\longrightarrow Cp_2ZrH(CH_2CH_2R)\bullet(Al_2H_5)$

$$Cp_2ZrH(CH_2CH_2R)\bullet Al_2H_5 \longrightarrow Cp_2ZrH_2\bullet Al_2H_4(CH_2CH_2R)$$

Thus far no detailed mechanism for the catalyzed process has been published, but there is general agreement that the reaction proceeds by formation of a complex transition metal hydride species, addition of this species across the olefinic double bond to give an organotransition metal species, and transmetalation to aluminum (See Scheme 2). Supporting evidence for each of these steps exists as follows:

1) Formation of a transition metal hydride species:

$Cp_2Zr(H)Cl$, a reagent used for hydrozirconation, is prepared by reaction of Cp_2ZrCl_2 with an aluminum hydride.[9] Cp_2TiCl_2 is reported to react with LAH to form a complex of molecular formula $Cp_2TiH(AlH_3)_2$.[10,11] The actual structure of this complex is not clear, but recent studies employing calorimetric titration have shown that the reaction proceeds in four steps, and that the complex composition is dependent on the LAH/Ti ratio until this ratio reaches 2.[12] A complex reaction pathway is proposed in which the final product is represented as a complex of AlH_3 with a species of composition $Cp_2TiH_2AlH_2$ in which two hydride bridges are proposed on the basis of EPR spectroscopic evidence (See Scheme III). Known cases of hydride bridging in mixed aluminum-zirconium complexes lend support to this hypothesis.[17]

Scheme III

$$2\,Cp_2TiCl_2 + LiAlH_4 \longrightarrow [Cp_2TiH_2AlCl_2\bullet Cp_2TiCl] + H_2 + LiCl$$

$$[Cp_2TiH_2AlCl_2\bullet Cp_2TiCl] + LiAlH_4 \longrightarrow (Cp_2TiH_2AlHCl)_2 + LiCl$$

$$(Cp_2TiH_2AlHCl)_2 + LiAlH_4 \longrightarrow ([Cp_2TiH_2]_2Al_2H_3Cl + AlH_3) + LiCl$$

$$([Cp_2TiH_2]_2Al_2H_3Cl + AlH_3) \longrightarrow 2\ (Cp_2TiH_2AlH_2 + AlH_3) + LiCl$$

2) Addition of transition metal hydrides to double bonds:

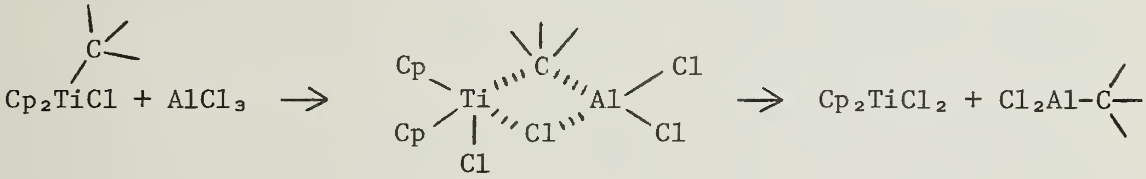
Low valent transition metal species are known to reduce double bonds.[11] Hydrozirconation is an obvious precedent which has achieved widespread attention. Reductions have also been achieved with low valent species of titanium, vanadium, iron, nickel, chromium, manganese, cobalt, copper, and zinc, all generated in situ by reaction of a metal halide with LAH.[11,13]

3) Transmetalation to aluminum:

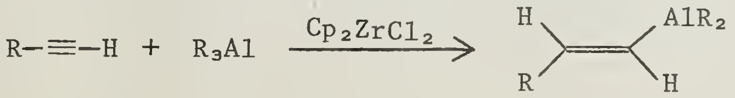
Schwartz and Carr have synthesized organoaluminum compounds by treatment of hydrozirconation reaction mixtures with $AlCl_3$.[14,15] Since they do not isolate the supposed alkylaluminum chlorides thus formed, it is not clear whether they are free or complexed with zirconium. The reaction products are those expected from organoaluminum intermediates, and are not produced under the same conditions in the absence of aluminum.

The transfer of σ-bound ligands to various electrophiles has been shown to proceed with retention of configuration at carbon.[15] This has been shown in the transmetalation to $AlCl_3$. The NMR spectrum of these transmetalation reaction mixtures, although exhibiting line broadening due to the quadrupole moment which prevents accurate determination of the extent of racemization, is consistent with this conclusion. This transfer of ligands is believed to occur via an alkyl-bridged intermediate such as that shown in Scheme IV.

Scheme IV



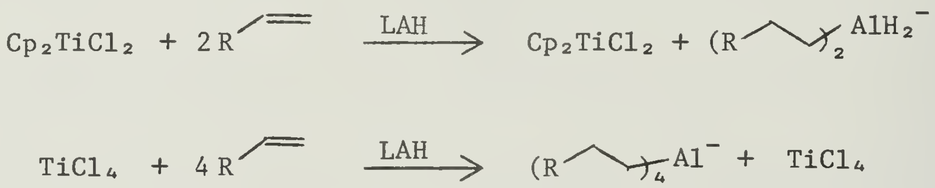
Most available evidence suggests that the active form of transition metal hydride generated is not free in solution, but remains complexed to aluminum in some way. Mixed titanium-aluminum complexes have been found to be homogeneous catalysts for the hydrogenation of olefins, a reaction which cannot be carried out with either metal alone.[16] In the carboalumination of terminal acetylenes with trialkylaluminums catalyzed by Cp_2ZrCl_2, neither trialkylaluminums nor aluminum-free alkylzirconium species such as $Cp_2Zr(R)Cl$ will effect the reaction, while a catalytic amount of Cp_2ZrCl_2 in the presence of R_3Al leads to reaction (Eq. 5). Additionally, reaction of either organoluminum or organozirconium compounds alone with terminal olefins is complicated by deprotonation to give terminally metalated acetylides, but with the mixed reagent, no acetylide formation is observed. Instead, an alkenylaluminum species and a small amount (5%) of an alkenylzirconium species are indicated by NMR spectroscopy.



(5)

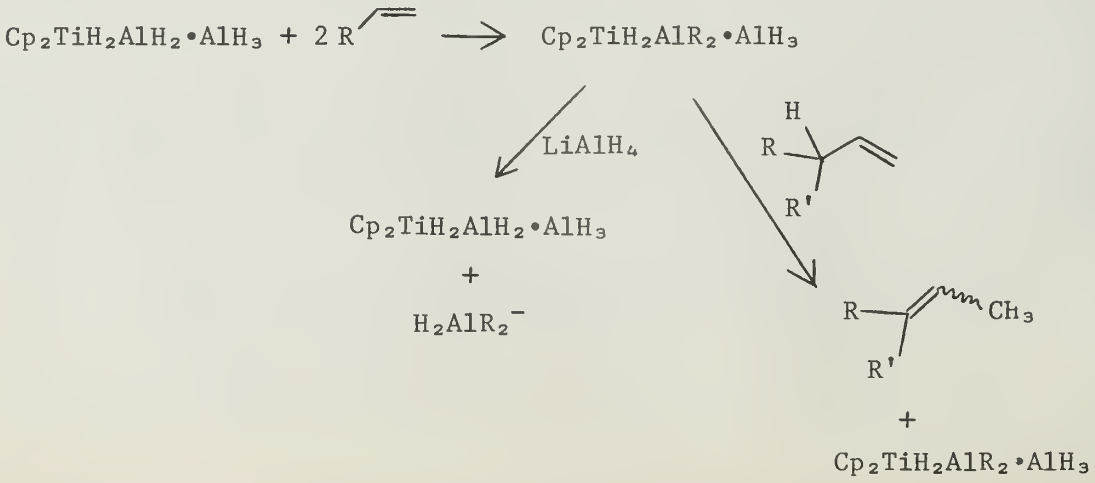
An interesting side reaction with some mechanistic implications occurs if an excess of olefin is used with one of the metallocene catalysts. Hydroalumination appears to proceed until two equivalents of olefin for each equivalent of LAH are consumed, and the recovered unreduced olefin undergoes isomerization.[2] Thus, 1-octene is converted to 2-octene in 80% yield by treatment with .05 equivalent of Cp_2TiCl_2 and .15 equivalent of LAH. Presumably the isomerization does not occur in the free organoaluminate species, since such species generated by other means do not isomerize. With $TiCl_4$ or $ZrCl_4$, four equivalents of olefin can be hydrometalated by each equivalent of LAH, and positional isomerization is not observed even at olefin:LAH ratios very close to 4[3] (See Scheme V). No studies have been reported using an olefin:LAH ratio greater than 4 with a metal tetrachloride catalyst.

Scheme V



The evidence is consistent with a process in which rapid hydrometalation by an aluminum-transition metal complex is followed by rapid transmetalation to give an organoaluminate. Dissociation of this complexed organoaluminate is necessary for catalyst turnover. When an excess of olefin is present, hydroalumination occurs to the extent that it can, and then the transition metal species promotes isomerization to the less reactive internal olefin, which presumably accumulates due to its kinetic stability (See Scheme 6). It appears that steric hindrance in the Cp_2TiCl_2/AlR_2H_2 complex prevents further alkylation of aluminum, presumably due to the bulk of the cyclopentadienyl ligands, since tetraalkylation occurs readily with $TiCl_4$ as a catalyst. The lack of such tetraalkylation with metallocene catalysts demonstrates that AlR_4^- is formed by transmetalation, and not by disproportionation of organoaluminum species.

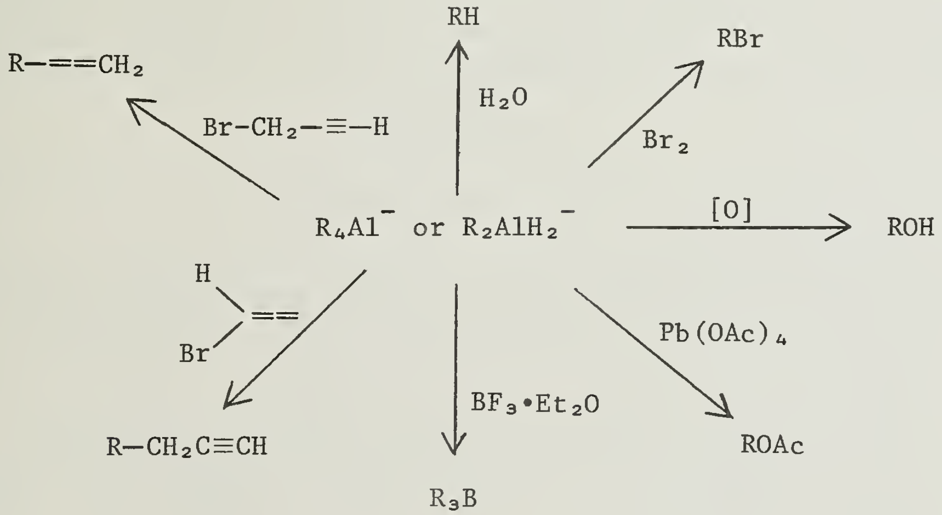
Scheme VI



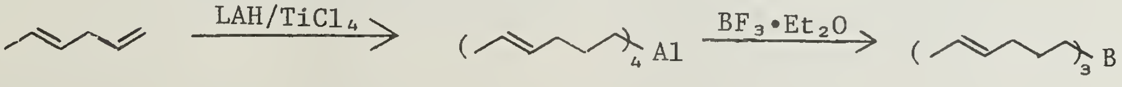
Synthetic Utility. Catalyzed hydroalumination of terminal olefins shows promise as a versatile method for the elaboration of double bonds into other functionalities, and for carbon-carbon bond formation. Hydrozirconation products are not generally effective nucleophiles for alkylation of carbonyl compounds or alkyl halides, although a few have been found to react sluggishly with acyl halides.[15] Hydroboration does not display the high selectivity for terminal olefins found in hydroalumination, and is thus not tolerant of other nonconjugated unsaturation elsewhere in a molecule. This selectivity, together with the rapidly expanding variety of uses to which organoaluminum compounds can be put, promises to encourage the widespread use of this reaction in synthesis.

Reactions of organoaluminum compounds have been known for some time, but have not been applied very much in synthesis due to the difficulty of obtaining the organoaluminum compounds. Thus, quenching of organoaluminum compounds with water provides a good method for selective reduction of terminal olefins, while halogenolysis gives 1-haloalkanes in high yields.[3-5] Oxidation with air,[4] or with peroxides or peracids,[18] affords alcohols. Reaction with lead tetraacetate gives acetates directly (See Scheme VII).[19] Many alkylations occur in good yield with organoaluminum compounds.[20]

Scheme VII. Some Reactions of Organoaluminum Compounds



The catalyzed hydroalumination reaction may also be used to prepare hitherto inaccessible alkenylboranes. Hydroboration of nonconjugated polyenes is relatively nonspecific, while specific hydroalumination of a terminal olefin in the presence of other unsaturation, followed by treatment with BF_3 etherate affords excellent yields of trialkenylboranes[21] (Eq. 6).



(Equation 6)

In a few cases cyclization of unconjugated polyenes has been observed during transmetalation from zirconium to $AlCl_3$, but these do not occur in catalytic systems using LAH.[15] Reaction of organoaluminates with 1-bromoallene yields terminal acetylenes,[22] while reaction with propargyl bromide gives terminal allenes.[23] Conversion to organocuprates gives coupling products, and in the presence of carbon monoxide leads to ketones. The conjugate addition of organocuprates to α,β-unsaturated carbonyls also occurs readily after formation of the organocuprates from organoaluminates.[26] The carbometalation of acetylenes leads to stereo- and regioselectively defined olefins, and may prove invaluable in terpene synthesis.[9]

A heterogeneous catalyst for hydroalumination has recently been prepared by linking $TiCl_4$ to silica gel, or Cp_2TiCl_2 to polystyrene.[27] This catalyst can be recovered and recycled by filtration prior to further reaction or quenching of the organoaluminates.

Titanium has also been found to catalyze hydroalumination with diaminoaluminum hydries,[28] and to catalyze hydroboration with borohydride.[29]

Since the catalyzed version of the hydroalumination reaction was discovered only recently, the applications in target-oriented organic synthesis are still few, and are primarily concerned with the conversion of terminal olefins to halides or alcohols, or with their reduction in the presence of other unsaturation. The reaction has been used in syntheses of recifeiolide,[30] and of Matsutake alcohol.[31] Further utilization of this reaction for a variety of transformations should follow rapidly.

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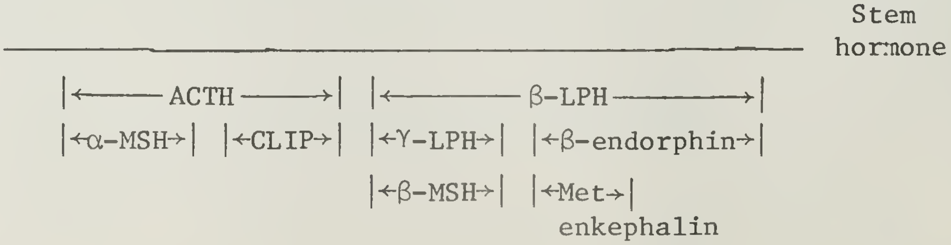
ENKEPHALINS AND ENDORPHINS, THE ENDOGENOUS OPIATES

Reported by John Lloyd February 25, 1980

For years, opiates have been known to produce the physiological effects of analgesia, antinoceception, and respiratory depression, as well as many other responses. Specific receptors in neuronal cells were postulated to mediate these responses and the first receptor model was proposed by Beckett and Casey in 1956.[1] When stereospecific binding of opiates to a receptor was established,[2] research intensified toward the isolation and characterization of the compounds which were the endogenous ligands of the opiate receptor. Li coined the term "endorphin" as a short from of endogenous morphine. In 1975, two compounds were isolated by Hughes.[3] They were two pentapeptides called enkephalins extracted from procine brain tissue which differed in their C-terminal residue. Methionine-enkephalin has the primary structure Tyr-Gly-Gly-Phe-Met and leucine-enkephalin has the structure Tyr-Gly-Gly-Phe-Leu. Both were found to be potent opiate agonists in vitro. The search for endogeonous opiates continued and in 1976 Li isolated another morphine-like polypeptide from both camel[4] and human[5] pituitary tissue which he named β-endorphin. This polypetide was sequenced and synthesized and was also found to be a very potent opiate agonist in vitro. The primary structure was that of a 30 amino acid chain in which the N-terminal residues were the same as methionine enkephalin. Subsequent research showed that the distribution of enkephalin immunoreactivity roughly parallels the distribution of opiate receptors.[6] Opiate receptor activity has been found generally throughout the brain and central nervous system but appears to be most concentrated at nerve termini. Enkephalins and endorphins have been isolated from brain tissue as well as from pituitary, hypothalmus and cerebrospinal fluid.[7,8]

Once the amino acid sequence of β-endorphin was known, indications of the biosynthetic origin of enkephalins and endorphins became apparent. Hughes observed that the sequence of methionine enkephalin was the same as the 61-65 residues of β-lipotropin (β-LPH).[3] Similarly, β-endorphin was found to have the same sequence as β-LPH (61-91).[4] Since that time, a precursor polypeptide has been isolated and sequenced[9] and the degradation products determined by pulse-chase labeling methods.[10,11] This molecule contains the sequences for both adrenocorticotropin (ACTH) and β-LPH (Figure 1). Subsequent inactivation of enkephalins and endorphins by proteolytic cleavage has been found to be very fast. In extracts of rat tissues the half-life of methionine enkephalin has been estimated to be 2-4 seconds.[12] Analogues of enkephalins with a D-Ala residue in the

Figure 1



second position have a high *in vivo* potency and duration of action[12] presumably due to increased resistance to proteolytic cleavage. It has been proposed that the protease is functionally linked to the receptor which may act as a concentrating mechanism to enhance the rate of proteolysis.[13]

Enkephalins and endorphins have been found to have assayable effects in a number of systems. Standard *in vitro* testing systems for opiates and opioid peptides include inhibition of electrically stimulated contractions of guinea pig ileum muscle and mouse vas deferens.[14] Competitive binding assays using either [^{3}H]-naloxone (a potent opiate antagonist) or [^{3}H] dihydromorphine (a potent opiate agonist) have been devised to test stereospecific receptor binding affinity.[14] The effect of sodium ion on binding forms the basis of an assay to determine relative agonist/antagonist potency. In competitive binding assays, a sodium concentration dependent shift toward lower binding affinities for agonists was observed while little change in binding affinity was found for antagonists.[15,16] The magnitude of this shift is between 10-60 fold for pure agonists and lower shifts are seen for compounds which display mixed agonist/antagonist behavior. This effect has been found to be specific for sodium ion and allows for a quantitation of relative agonist/antagonist potency.

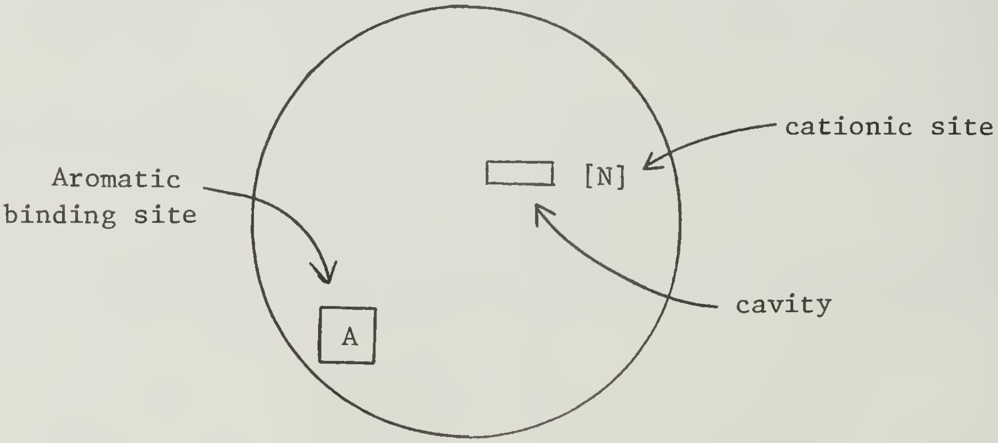
Although enkephalins and endorphins were first discovered in conjunction with their opiate-like analgesic effects, these or any other effects observed in an isolated system may or may not bear on their true *in vivo* role. Enkephalins and endorphins have been implicated in a wide range of biological responses. Elevated levels of enkephalins have been found in animals suffering from shock[17] and stress.[18-21] Conflicting evidence exists on the postulated role of enkephalins in the transmission of pain. Although *in vitro* studies suggest that enkephalins inhibit the transmission of pain across the synapse of neurons,[22] studies in humans have found that injection of an enkaphalin antagonist (naloxone) had no effect on pain perception.[23] Additional studies have implicated enkephalins and endorphins in the regulation of pancreatic secretion of insulin and glucagon[24] as well as mediating pleasure and euphoria[25] and overeating.[26]

The results of the distribution studies and pharmacological testing suggest that enkephalins and endorphins may act as neurotransmitters or neuromodulators. This view is supporte by the known effect of opiates to inhibit the release of acetylcholine[27] and noradrenaline.[28] When neuronal tissues are depolarized by addition of high concentration of potassium, a large increase in the methionine enkephalin flux is observed;[29,30] which is characteristic of neurtransmitters in the central nervous system.[29] Both opiates and β-endorphin inhibit calcium uptake in neurons and may thus inhibit the release of neurotransmitters.[31] Morphin has been observed to inhibit the potassium evoked release of substance P, the putative pain neurotransmitter.[22] In addition to direct acting effects on neurons, enkephalins and endorphins may act through inhibition of adenylate cyclase.[14] Recently, the inhibition of adenylate cyclase by opiates has been found to have an absolute dependence on sodium and GTP.[32] It has been proposed that interactions with the opiate receptor are transmitted to the catalytic unit of adenylate cyclase through membrane bound coupling molecules and that the action of these couplers is mediated through the binding of sodium and GTP.[1] No evidence has yet linked this sodium requirement and the effect of sodium on agonist binding affinity. Due to the greater metabolic stability of β-endorphin,[12] enkephalins and endorphins may have different physiological roles with the enkephalins acting at the neurons and endorphins acting at peripheral sites. For a further understanding of the mode of action and pharmacological properties of opiates and opioid peptides, we must look at the receptor-ligand interaction.

The correlation of the structures of opioid peptides and the active site of the receptor would be a difficult task in such conformationally mobile systems. Because the enkephalins and opiate agonists and antagonists bond to the same receptor, opiates may be used as a model system for mapping the receptor. Fortunately, many highly active opiates are very conformationally rigid and thereby provide excellent receptor probes. The criterion for judging the validity of each proposed receptor model must be that it accounts for the differentiation of agonists and antagonists and allows for partial agonist/antagonist behavior, it must account for the sodium effect, and it must explain the activity of a large range of known opiates of widely varying structure.

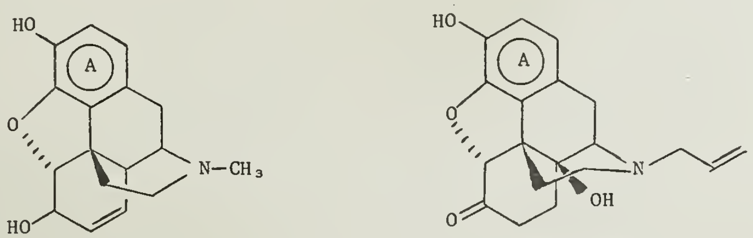
The first and simplest model was proposed in 1954 by Beckett and Casey.[1] They had noticed several interesting aspects of opiate activity which included a high degree of stereoselectivity for both agonists and antagonists and that receptor fit did not imply agonist activity since antagonists also fit and bond to the receptor. From comparing the structures of several agonists and antagonists, they proposed that the common features necessary for binding were a tertiary basic group and a flat aromatic ring structure. They postulated a three-point attachment model in which a third structural feature, such as a hydrocarbon moiety, confers stereospecificity. These structures have the relative orientation to accomodate morphine (Figure 2). The hydrocarbon binding site is in the form of a cavity that can accomodate the protruding piperdine ring perpendicular to the phenolic ring. This model is suitable to explain the bonding of morphine and morphine's analogues, but it cannont account for the binding of other known opiates in which the phenolic ring is held in a different orientation relative to the tert nitrogen and piperdine ring (*e.g.*, N-methylphenylmorphan). It also did not account for differentiation between aganosits and antagonists and it did not address the yet undiscovered sodium effect.

Figure 2



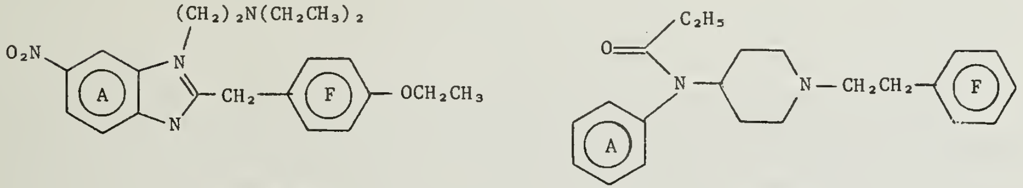
In 1976, Snyder proposed a model which accounted for the greatly enhanced potencies of the newly synthesized oripavines and thebains as well as agonist/antagonist behavior and the sodium effect. It was observed that the most powerful opiates (such as etonitazene, phenazocine, 7-[1-phenyl-3-hydroxybutyl-3]endoethenotetrahydrothebaine (PET) and fentanyl) contained a second aromatic ring, F (Figure 3). It was proposed that the receptor has not only a lipophilic center to interact with the A ring and an anionic center to attract the nitrogen, but also posessed a third site to which the F ring of agonists could bind. The receptor was presumed to exist in two conformations, agonist and antagonist, which interconvert through the binding of a sodium ion. At physiological sodium concentrations, the receptor would be in the antagonist conformation and the binding of an agonist would cause transformation to the agonist conformation. Agonists such as morphine which do not have an F ring will have only moderate potency while the enhanced potency of molecules such as PET is derived from further stabilization of the agonist by the F ring interaction. An N-allyl substituent has long been known to change an agonist into an

Figure 3



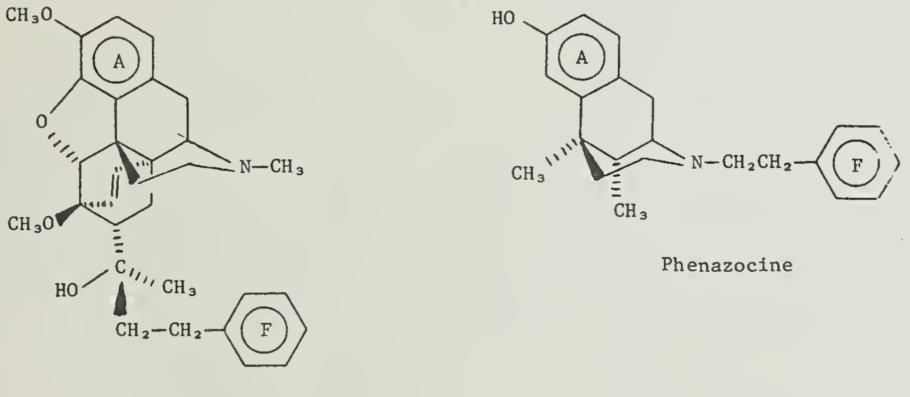
Morphine

Naloxone



Etonitazene

Fentanyl

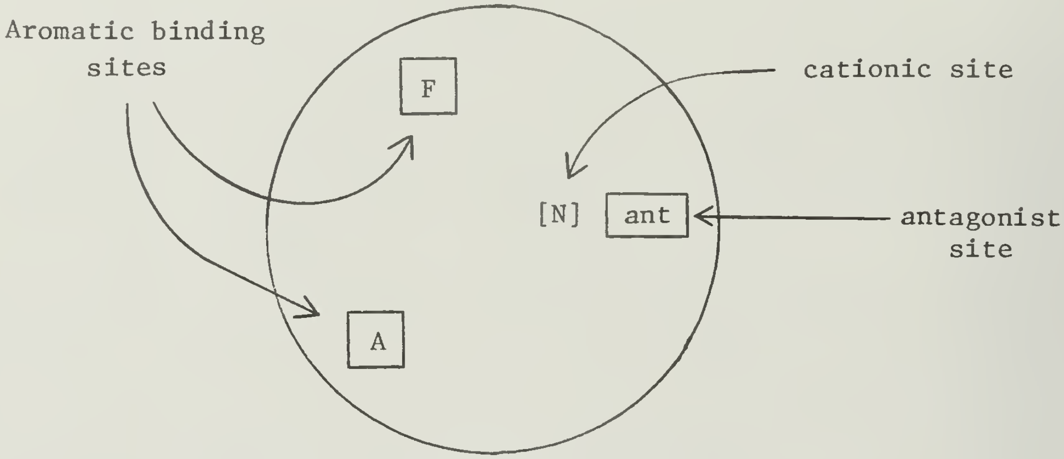


PET

Phenazocine

antagonist in many cases. This behavior can be explained by an antagoist site suitably positioned to interact with the N-allyl substituent (Figure 4). Compounds in which the nitrogen configuration is locked so as to interact with the antagonist site will be pure antagonists, while those in which inversion at nitrogen can occur may exhibit partial agonist/antagonist behavior.

Figure 4



While the Snyder model accounted for a great deal of the known data, some modifications were made by Galt to give it even wider applicability.[34] In several cases poor stereoselectivity of binding was observed and both enantiomers of an opiate displayed potent effects. By extending the hydrophobic binding area of the A ring in Snyder's model, the binding of several anamolous compounds could be explained.

A different model was proposed by Kolb that disagrees with the Snyder model on a number of points.[35] She argues that the unprotonated form of the molecule binds to the receptor and it is the orientation of the lone pairs that determines the agonist or antagonist effect. For an antagonist interaction, the lone pair should be oriented toward the receptor. She contends that by qualitative conformational analysis of naloxone, the lowest energy conformation for the piperidine ring would be skew boat with the N-substituent pseudoequatorial to allow for greatest rotational freedom, and the lone pair in a position to interact with the antagonist binding site. In the case of oxymorphone, the most stable conformation is boat in which the N-substituent is equatorial and the lone pair points in the axial direction and can interact with an appropiate agonist binding site. Compounds that can easily exist in both conformations can exhibit mixed agonist/antagonist activity.

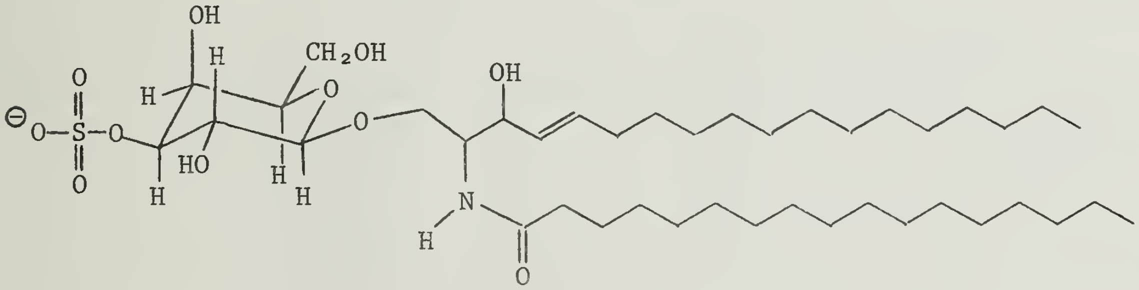
Kolb's model can be argued on several points. She assumes the receptor conformation of the ligand to be the one of lowest energy; however, if conformational interconversion is facile conpared to receptor binding, then the relative energies will have no bearing on the conformation at the receptor. Conformational analysis must be used with caution when applied to receptor mapping since it required that the barriers to interconversion be large relative to the kinetic barrier to receptor binding.

Loew and Berkowitz have also done conformational analysis by quantum chemical methods on several opiates, including nalozone and oxymorphine, and have found the lowest energy conformation at the piperdine nitrogen to be equatorial.[36] In addition, a correlation between relative agonist/antagonist behavior and the relative energies of the equatorial and axial N-substituent confromations was found not to exist. Loew and Berkowitz have also done quantum chemical calculations on the conformations of oxipavines and have further refined Snyder's model to account for stereoselectivity at the C-19 carbinol position.[37] They suggest that intramolecular hydrogen bonding between the C-19 OH and C-6 OCH_3 fixes the conformation at C-19. Optimum interaction between the C-19 substituents and a lipophilic area on the receptor (F in the Snyder model) is the primary event in directing opiate binding.

Some interesting structure activity studies have been done by Portoghese in which he uses stereoisomeric methadones and 4-phenylpiperdines to asses the stereo requirements of the opiate receptor.[38] His studies indicate that the conformation of these flexible opiates is integrally related to their chirality. He suggest that configuration and conformation must be examined together to account for the stereochemical preferences in receptor binding. A model is also proposed in which multiple modes of interaction with the receptor are possible in order to accomodate the more flexible opiates. The multiple modes hypothesis may also explain the inversion of absolute stereochemical preference between classes of opiates.

An even more specific model has been proposed by Loh in which he proposes cerebroside sulfate as the actual membrane bound receptor[39] (Figure 5). Cerebroside sulfate has been implicated in stereospecific opiate binding in several investigations.[40,41] Loh proposes interaction of the phenyl group with the amide π system, ionic interaction of the nitrogen with the sulfate group and hydrogen bonding of other polar groups on the opiate with the hydroxyl group of the sugar. The most significant advantage of this model is its flexibility to accomodate many structurally diverse opiates. It may also allow for the multiple modes of receptor interaction proposed by Portoghese. Loh also proposes a novel mechanism for differentiating between agonists and antagonists based on an ion pair mechanism. Antagonists are characterized by forming a solvent separated ion pair between the cationic nitrogen and the sulfate while agonists form an intimate ion pair. The solvent separated ion pair is considered to be hydrophilic relative to the intimate ion pair. The

Figure 5. Cerebroside sulfate



action of opiates is then mediated through modification of the hydrophobic-hydrophilic balance of the receptor and the associated membrane.

All of these models are useful to some degree in that they explain some aspect of opiate structure-activity relationships. Their applicability may be more rigorously tested by their ability to make predictions about new synthetic opiates and to explain the effects of endorphins and enkephalins. To determine the structural similarities between enkephalins and opiate, several structure activity studies were done using synthetic enkephalin analogues. Initial studies[3,42] observed the correspondence of the terminal nitrogen and the phenolic ring of tyrosine with the phenolic ring and piperdine nitrogen of morphine. This "tyramine" moiety forms the basis of most comparisons of enkephalins and opiates. Studies have found that blockage of the amino terminus of methionine-enkephalin had little effect on activity; substitution of phenylalanine for tyrosine (1) or L-alanine for glycine (2) resulted in analogues of no or low activity.[43,44] Interestingly, it was observed that substitution of D-alanine for glycine (2) resulted in a compound of high receptor affinity as well as long acting, presumably due to its resistance to proteolytic degradation.[45] Structure-activity studies has been done in which α-methylated amino acids have been substituted into enkephalins and some of these analogues have shown biological activity.[46] The proposed receptor conformation of of enkephalins must allow for the accomodation of the methylated amino acids in the biologically active cases and must not allow these amino acids in the inactive cases as well as compare favorably to the rigid opiates.[46]

Information on enkephalin conformations is available from several sources, X-ray crystal data,[47] NMR[48-51] and circular dichroism[52] solution studies and theoretical calculations.[53,54] These techniques have not yet been able to propose a structure that is entirely consistent with the structure activity data. Gorin et al.[46] have used the rigid opiates as a model to propose a receptor bound confomation which is consistent with the known structure activity data. Verification of this conformation depends on its utility to predict and explain further structure activity data.

The same difficulties in predicting the enkephalin receptor conformation is encountered with β-endorphin. Although naethionine enkephalin and β-endorphin have approximately the same in vitro potency, α-endorphin (β-LPH (61-76)), γ-endorphin (β-LPH (61-77)) and β-LPH (61-87) have considerably decreased activity.[55] To further complicate endophin and enkephalin structure-activity studies, not only may there be multiple modes of receptor ligand interactions as proposed by Portoghese, but there has been established that multiple forms of the opiate receptor exist, each with somewhat different selectivity for opioid ligands.[56-60] In addition, a depeptide (L-Tyr-L-Arg) has been found to have potent opiate effects.[61,62] It has yet to be established whether this substance interacts at the opoid receptor or acts at the site of endorphin or enkephalin biosynthesis as a releasing factor.

Continued research with opiates and opioid peptides promises improved receptor models and isolation of the receptor which may lead to improved opiate or peptide pharmaceuticals. Research into the physiological role of endorphins and enkephalins should yield valuable insight into the mechanism of stimulus transmission in the central nervous system.

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PHOTOCHEMICAL ELECTRON-TRANSFER REACTIONS IN MICELLES

Reported by Peter B. Grasse February 28, 1980

Photosynthesis has intrigued man for centuries. Presently proposed mechanisms for photosynthesis implicate a scheme of photoinitiated electron-transfer reactions; the chemistry is complicated by the chloroplast's complex membrane architecture. A rational chemical 'first prototype' for a photosynthetic model is the examination of the electron-transfer chemistry associated with micelles. Here the chemist has the opportunity to gain useful information from a relatively simple system. This report will review important properties of micelles, aspects of photoinitiated electron-transfer chemistry, and recent examples of photoinitiated electron-transfer reactions associated with micelles.

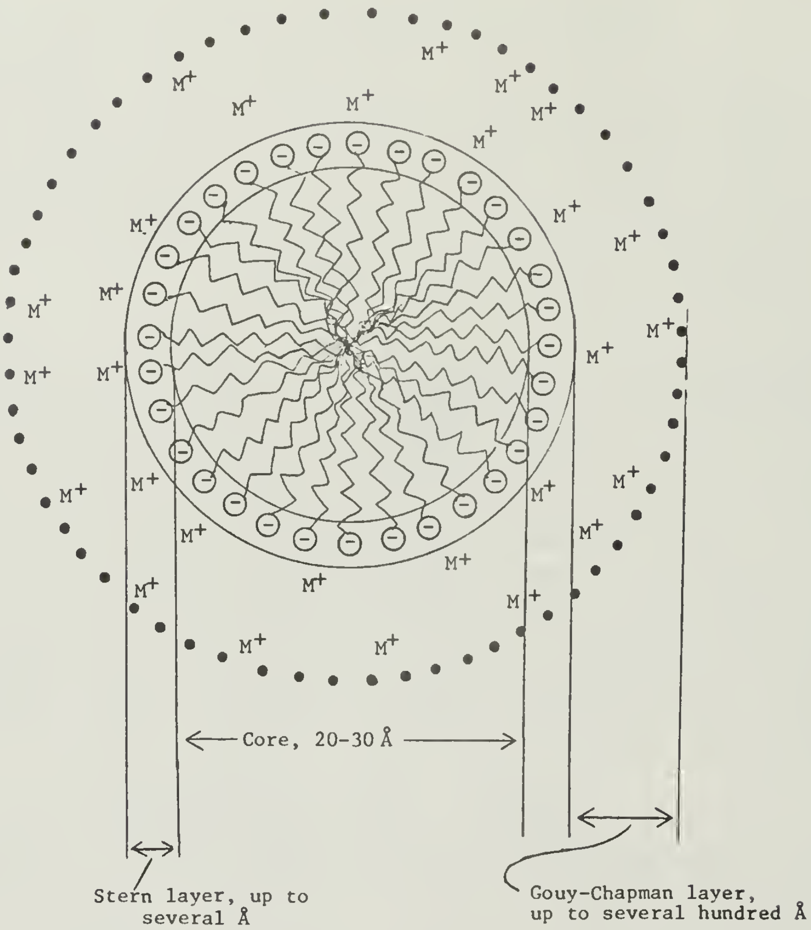
Micelles.[1] A micelle is an organized aggregate of between 30 and 150 surfactant molecules. The surfactant molecules, often called monomers, are composed of polar hydrophilic groups called heads and nonpolar hydrophobic groups called tails. Surfactants are classified into four groups according to the identity of the head: cationic, anionic, nonionic, and zwitterionic. Cationic surfactants can be represented as $R_nX^+Y^-$. X is typically N, S, or P. Anionic surfactants are typically salts of carbon, sulfur and phosphorous acids. Nonionic surfactants are usually alcohols, amides, amines, esters, mercaptans, or oxides. Zwitterionic surfactants possess potential cationic or anionic moieties whose charge is determined by the pH of the medium. The tails of all the above classes of surfactants are long hydrocarbon chains. Table 1 contains a list of some common surfactants.

Table 1. Common Surfactants

Compound Name	Abbrev.	Formula
Sodium dodecyl (lauryl) sulfate	SDS(NaLS)	$CH_3(CH_2)_{11}OSO_3Na$
Cetyltrimethylammonium bromide	CTAB	$CH_3(CH_2)_{15}N^+(CH_3)_3{}^-Br$
Sodium cetyl sulfate	NaCS	$CH_3(CH_2)_{15}OSO_3Na$
Europium decyl sulfate	$Eu(DS)_3$	$(CH_3(CH_2)_9OSO_3)_3Eu$
β-D-octyl glucoside		$C_8H_{17}OCHC_5H_{10}O_5$
Brij 35		$C_{12}H_{25}(OCH_2CH_2)_{23}OH$
Dodedecy N-betaine		$C_{12}H_{25}N^+(CH_3)_2CH_2COO^-$

A micelle is thought to be an essentially spherical or ellipsoidal aggregate of the monomers. The polar head groups are believed to be held on the surface of the micelle (Figure 1). The micelle's structure has been divided into two broad regions: the interior and the exterior or Stern layer. The interior contains the hydrophobic hydrocarbon chains. The Stern layer is composed of solvated head groups and bound solvated counterions. Surrounding the Stern layer is a diffuse double layer of unbound counterions known as the Gouy-Chapman layer.

Figure 1. Micelle Cross Section


M^+
Core, 20-30 Å
Stern layer, up to several Å
Gouy-Chapman layer, up to several hundred Å

When the monomer concentration exceeds the critical micelle concentration (cmc), micelle formation occurs. It is generally assumed that below the cmc, no micelles exist and above the cmc, changes in the monomer concentration effect only the number of micelles while the concentration of unassociated monomer is unchanged. The cmc for a system can be determined by noting a drastic change in some property of the solution (e.g. conductance, viscosity, pH, light scattering, etc.) as a function of monomer concentration. The evidence indicates that the micelles are in constant dynamic equilibrium with the bulk aqueous phase and the half-life for monomer exchange is in the microsecond time domain. Thus, for the very fast electron-transfer events discussed below, we can consider the micelle as a static entity.

One of the first recognized properties of micelles is their ability to solubilize hydrophobic compounds in aqueous solution. For example, the solubility of pyrene in water is changed from 6×10^{-7} M to 7×10^{-2} M by the addition of 0.04 M sodium lauryl sulfate (NaLS). The solubility of pyrene in the micellar solution is comparable to its solubility in hydrocarbon solvents. Solute-micelle association constants are typically in the range of 10^4 to 10^5 M^{-1}. Grieser and Thomas[2] estimate the average residence time of solubilized arene compounds to be in the microsecond time domain.

Much still needs to be learned about the detailed structure of micelles. Some areas now under active investigation are the properties of water within the micelle,[3] the dividing line between the micelle's interior and the Stern layer,[4] the location[5] and movement[6] of solutes within a micelle, the physical properties of the interior,[7] and the effect a solute has on a micelle's structure.[8]

Electron-Transfer Reactions of Excited States.[9] Mataga[10] and Weller[11] have shown that electron transfer can be a common reaction path of excited state species. Absorption of a photon produces a species that is both a more powerful oxidant and reductant than the ground state species. The photon's energy excites an electron to a higher level where it is more weakly bound, while an electron hole is simultaneously produced in a lower level. The thermodynamics of the reaction are described for the generalized case (Equation 1) in Equation 2, where E_{ox} is the oxidation potential of the donor (D), E_{red} is the reduction potential of the acceptor (A), E_{coul} is the coulombic energy term, and $\Delta E_{o,o}$ corresponds to the electronic excitation energy. The kinetics of these excited-state electron-transfer reactions can be studied using the usual Stern-Volmer fluorescence quenching analysis. Meyer[12] has extended these ideas for the prediction of excited-state redox potentials from electron-transfer rate constants.

$$A + D \xrightarrow{h\nu} A^{\dot{-}} + D^{+\cdot} \tag{1}$$

$$\Delta G = C[E_{ox} - E_{red} - E_{coul}] - \Delta E_{o,o} \tag{2}$$

The radical pairs produced in these reactions are high-energy species capable of redox chemistry with other molecules. However, geminate recombination of the radical ion pairs to regenerate ground state starting material usually occurs with high efficiency. Thus, to efficiently convert photons into a chemical potential, the back-electron-transfer reaction must be controlled and, as the following examples illustrate, ionic micelles can potentially do just that.

Electron-Transfer Reactions in Micelles. Thomas[13] has examined the dynamics of excited-state charge-transfer complexes in miceller media. Pyrene (Py) fluorescence is efficiently quenched by N,N-dimethylaniline (DMA) in a micellar solution. The lifetime of Py^{*1} is described by a single exponential decay. NMR and fluorescence techniques suggest Py is solubilized in the micelle's interior.[14] Since the DMA electronic absorption spectrum in micellar media resembles that observed in water rather than the spectrum observed in nonpolar solvents, Thomas[13] concludes with supporting NMR data[14] that the DMA is solubilized in the Stern layer.

A Stern-Volmer plot of I_o/I_f vs. [DMA] shows curvature indicating the fluorescence-quenching rate constant, K_q, is dependent on [DMA]. To understand the anomolous behavior we need to examine the extent of association of DMA with the micelle. If we assume that the concentration of micellized DMA, ($[DMA_m]$), reaches some limiting maximum value and that quenching of micellized Py^{*1} can occur only by DMA_m,[15] then the following scheme explains this behavior.

$$\mathrm{DMA} \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} \mathrm{DMA_m} \qquad (3)$$

$$\mathrm{Py}^* + \mathrm{DMA_m} \xrightarrow{k_2} \mathrm{DMA}^{+\cdot} + \mathrm{Py}^{\dot{-}} \qquad (4)$$

$$\text{Quenching Rate} = k_q\,[\mathrm{DMA_m}]\,[\mathrm{Py}^{*1}] \qquad (5)$$

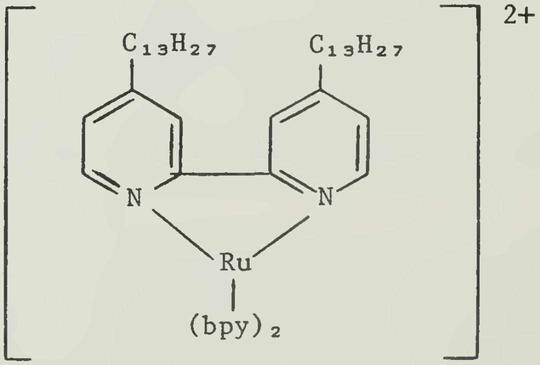
$$\text{at low [DMA], } [\mathrm{DMA_m}] = \frac{k_1}{k_{-1}}\,[\mathrm{DMA}] \qquad (6)$$

$$\text{at high [DMA], } [\mathrm{DMA_m}] = [\mathrm{DMA_m}]_{\max} \qquad (7)$$

The fate of the micellized radical ion pair $(\mathrm{Py}^{\dot{-}}\ \mathrm{DMA}^{+\cdot})_m$ produced in reaction 4 depends on the micellar environment. In cationic micelles such as CTAB, the $\mathrm{DMA}^{+\cdot}$ is rapidly expelled from the micelle surface due to strong coulombic repulsive forces. Transient absorption spectroscopy can be used to monitor the relatively slow decay of $\mathrm{Py}^{\dot{-}}$. In anionic micelles such as NaLS the coulombic interactions bind the $\mathrm{DMA}^{+\cdot}$ to the micelle's surface. In this case geminate recombination is observed, characterized by an initial fast decay of $\mathrm{Py}^{\dot{-}}$, followed by a slower decay similar to that observed in cationic micelles.

It is interesting to compare the lifetime of the $\mathrm{Py}^{\dot{-}}$ that has escaped geminate recombination in ionic and nonionic micelles. Both cationic and anionic micelles significantly enhance the lifetime of $\mathrm{Py}^{\dot{-}}$ as compared to nonionic micelles indicating the importance of the micelle's surface charges as a permeability barrier to charged species.[14]

Functionalized Micelles. 1. Surfactant Ru^{2+} Species. Whitten[20] has incorporated the surfactant derivative 1 into cationic and anionic micelles. The excited state of 1 is quenched by the dimethylviologen



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cation (DMV^{2+}) (which is believed to bind on the micellar surface) via electron transfer. In cationic micelles quenching occurs at a rate slower than in homogeneous solution. This can be explained in terms of a coulombic barrier hindering the approach of the cation to the micelle. Conversely, in anionic micelles the quenching is greatly enhanced compared to homogeneous solution.

Whitten also observed that an increase in surfactant concentration (above the cmc) leads to decreases in the Stern-Volmer quenching constant suggesting that micelle bound DMV^{2+} participates in the quenching process. The quenching rate constant is also dependent on ionic strength, the former increasing as the latter decreases. This seems to indicate that the DMV^{2+} must compete with sodium ions for sites on the micelle surface.

Matsuo _et al._[21] examined a similar Ru^{2+} surfactant system with DMV^{2+} observing the decay of the intermediates which supports Whitten's work.

2. _Reactive Metal Counterions_. Grätzel[16,17] has reported studies of light-initiated electron-transfer reactions where the micellar counterion has the potential to be a reactive species. N-methylphenothiazine (MPTH) is photolyzed by a 15 nanosecond laser pulse (347.1 nm) in metal ion lauryl sulfate (MLS) micelles. Absorption of a photon rapidly produces a triplet species ($MPTH^{*3}$). End of pulse transient absorption spectroscopy is used to monitor the behavior of $MPTH^{*3}$ with various metal ions as counterions for the micelles.

When Na^+ is the counterion, the end of pulse spectrum is that of the $MPTH^{*3}$ ($\phi_T \approx 1$, $T_{\frac{1}{2}} \sim 1\,ms$). Deactivation via triplet-triplet annihilation is greatly retarded due to the sequestering of the species in a micelle.[15] When Co^{2+} or Ni^{2+} are used as counterions, heavy atom deactivation of the $MPTH^{*3}$ is observed as shown in Equation 8. The

$$MPTH^{*3} + M^{2+} \longrightarrow MPTH + M^{2+} \qquad (8)$$

quenching ratio (Ni^{2+}/Co^{2+}) observed in homogeneous solution is maintained in micellar solution. This indicates that the $MPTH^{*3}$ lifetime does not depend only on diffusion of the triplet to the micellar surface. Grätzel also concludes that due to the extremely fast nature of the triplet deactivation the MPTH must be solubilized near the micelle-water interface.[16]

When Cu^{2+} is used as the counterion, no $MPTH^{*3}$ can be observed in the end of pulse spectrum; rather, the radical cation ($MPTH^{+\cdot}$) is observed, indicating rapid oxidative quenching of $MPTH^{*3}$ occurred via reaction 9. This process occurs with a remarkably high quantum efficiency

$$Cu^{2+} + MPTH^{*3} \longrightarrow Cu^{+} + MPTH^{+\cdot} \qquad (9)$$

of 0.93. Almost exclusive production of $MPTH^{+\cdot}$ is a result of micellar enhancement of reaction 9 due to the very high local concentration (estimated between 3 and 6 $\underline{M}$[18]) of Cu^{2+} in the Stern layer.

The decay of $MPTH^{+\cdot}$ is characterized by fast second order kinetics indicative of an intermicellar quenching mechanism. Grätzel postulates Cu^+ is rapidly displaced from its original micelle by a Cu^{2+} which is present in high local concentration in the Gouy-Chapman layer.[16] The Cu^+ undergoes random diffusion until it encounters a micelle-$MPTH^{+\cdot}$ complex where quenching can occur.

Since Eu^{2+} species have shown promise in solar energy schemes,[19] Grätzel examined micelles with Eu^{3+} as the counterion. However, since the Krafft point (temperature above which micelle formation can occur) of $Eu^{3+}(DS)_3$ is too high to prepare micellar solutions of the surfactant at room temperature, Gratzel prepared mixed micelles of $Eu^{3+}(DS)_3$/NaLS or /$Zn(LS)_2$ (with Eu^{3+}/metal ion $\approx$ 0.6).[17] Laser flash photolysis of MPTH in such micelles leads to the production of $MPTH^{+\cdot}$ via oxidative quenching of $MPTH^{*3}$ by the Eu^{3+} with a very high quantum efficiency.

The decay of the $MPTH^{+\cdot}$ via back electron transfer with Eu^{2+} can be described in terms of a fast intramicellar geminate recombination characterized by first-order kinetics and a slower intermicellar recombination characterized by second-order kinetics. Note for the case with Cu^{2+} as the counterion only the latter second-order process was observed. Interestingly, the fraction of Eu^{2+} to be quenched in a geminate intramicellar process is dependent on the identity of the co-counterion and is much larger for Na^+/Eu^{3+} micelles than for Zn^{2+}/Eu^{3+} micelles. Presumably, the Zn^{2+} is more effective in replacing Eu^{3+} than Na^+. This exchange depends on the charge of the ions involved and the potential decay of the electrical double layer for the micelle.[17] In the case of $Cu^{2+}(LS)_2$ micelles, these factors are particularly favorable, allowing very fast (1 ns) replacement of Cu^+ by the Cu^{2+}.

Conclusion. The use of micelles for the specific solubilization of one member of a photo-redox pair offers the chemist a means to control to some extent the back electron-transfer reaction to regenerate ground state starting material which limits efficiency. To take advantage of this control, the radical ions must be recycled to ground state starting material via a pathway that is able to utilize in some fashion the energy difference between the radical ions and ground state starting material.

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CARBON ISOTOPE EFFECTS IN ENZYMATIC REACTIONS

Reported by Adrienne Tymiak March 6, 1980

Enzymes catalyze reactions with unparalleled efficiency in substrate recognition,[1,2] stereochemical control,[3] and rate enhancement.[4] Investigations of enzymatic mechanisms should therefore provide valuable information with applications to physical, synthetic, and bioorganic chemistry.[5-7] Traditionally, isotopic substances have been employed as non-perturbing tracers in the study of enzymes.[8] However, upon closer examination, enzymatic reactions are observed to discriminate between isotopes on the basis of mass differences.[9,10] Such isotopic effects on kinetic rates and on equilibria have been particularly valuable in providing specific mechanistic information.[5] Originally, only hydrogen isotopes were used.[11,12] With the increased availability of heavy atom isotopes and refined analytical techniques, studies of isotope effects on enzymatic mechanisms have been extended to include other nuclei of bioorganic interest.[13,14] A review of the measurement and interpretation of carbon isotope discrimination by enzymes follows.

Theory. The current transition state theory predicts carbon and hydrogen kinetic isotope effects to be qualitatively comparable.[14] This theory states that the rate constant, k, for a simple reaction is a function of the activation energy, E_a, defined as the energy required to excite the reactant from its ground state (S_o) to the transition state ($S^{\ddagger}$). An isotopic substituent may shift the energy of the transition state relative to that of S_o. Thus, if a bond to an isotope is partially formed or broken in the transition state, a change in E_a may result. Although a heavy isotope substitution will lower the S_o energy (vibrational frequency) of a bond,[14] the corresponding bond energy in the transition state structure may be either decreased or increased. The magnitude and direction of a carbon isotope effect will then depend on the relative curvatures of ground and transition state potential energy minima (Figure 1).[8]

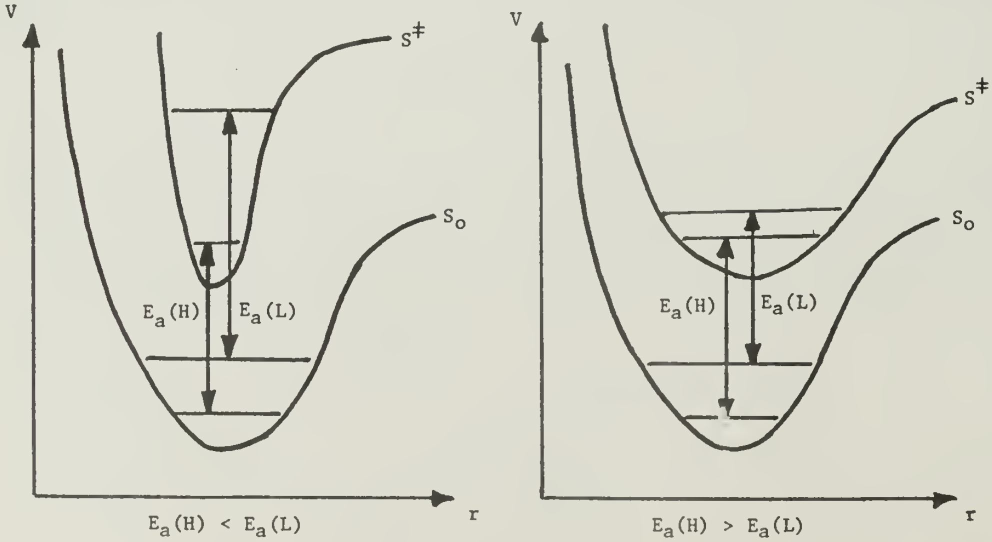


Figure 1. Theoretical examples of relative bond energies for a light (L) and a heavy (H) isotope.

By analogy to hydrogen transfer reactions, the magnitude of carbon kinetic isotope effects has been correlated to the degree of bond breakage (or Pauling bond order) in the transition state.[4,15-17] Model calculations and reactions have indicated that a maximum effect can be expected for symmetrical S_N2 transition states.[14,16,18] A dissimilarity between carbon and hydrogen isotope effects occurs since carbon is seldom an end atom. Corrections must be made for stretching and bending interactions between the atoms bonded to carbon because of their contribution to the stability of the more complicated transition state.[19]

Multistep reaction pathways further complicate the analysis of kinetic isotope effects. In many cases,[20] enzymic reactions are adequately described by simple Michaelis-Menten kinetics. O'Leary[4] has applied this approximation to enzymatic decarboxylation reactions (Eq. 1), assuming k_3 to be the only isotope-dependent rate parameter. Equilibrium isotope effects have been described[14,15,21-25] and so the inclusion of these effects on k_1 and k_2 should provide a better model of enzymatic decarboxylations.[26] Methods of deriving rate equations for more complex enzymic mechanisms have been reviewed.[27]

$$E + S \underset{k_2}{\overset{k_1}{\rightleftharpoons}} E \cdot S \xrightarrow{k_3} E \cdot P + CO_2 \qquad (1)$$

Current models of enzyme catalysis imply that there need not be a single rate determining step. Instead, enzymes may operate by converting substrates to products via a series of steps with similar activation energies. The highest energy transition state in the model mechanism may involve solvent reorganization, physical interactions in the enzyme complex, or molecular conformation changes, rather than formal changes in bonding.[6,7] The observed isotope effect would then be a weighted average of all the steps comparable in energy to the actual rate determining step.[17,28] Yet, a measured isotope effect can still imply that bond formation or breaking is at least partially rate limiting. In this case, the observed isotope effect also characterizes what might be thought of as a virtual or effective transition state for the overall kinetic mechanism. The simplicity of such an interpretation may be advantageous.[10]

Measurement of Carbon Isotope Effects. Carbon isotope effects are determined by comparing reaction rates of $^{12}_{6}C$ and one of its isotopes (Table 1).[29] Since ^{11}C is both expensive and short-lived, its routine use

Table 1

Isotope	Mass (amu)	Relative Natural Abundance	Half life ($t_{1/2}$)
$^{11}C_6$	11.011431	-	20.3 min
$^{12}C_6$	12.000000	100	stable
$^{13}C_6$	13.003355	1.12	stable
$^{14}C_6$	14.005241	-	5730 yrs

is impractical. Although the radioisotope ^{14}C is reasonably available, at high concentrations it may cause significant radiation damage to the experimental enzyme system. The best candidate for isotope effect measurement is ^{13}C, since it is stable and naturally occurring. It has been suggested, however, that the nuclear spin of ^{13}C may contribute to observed k_{13} (the rate constant for a ^{13}C-labeled compound) values,[30] especially in reactions with radical pair intermediates.[31,32] The magnetic spin contribution may be resolvable by comparison of three isotopic rate constants (k_{12}, k_{13}, k_{14}) although this approach has not yet been tested.[30] Hydrogen isotope effects, while largest in magnitude,[14,25,33] are subject to problems involving positional lability[34,35] and enzyme tolerance limits.[10,36] In these respects, ^{13}C isotope studies prove superior despite their relatively small magnitude.

The measurement of carbon kinetic isotope effects relies on analytical precision. Direct measurements of k_{12} and k_{13}, separately, provide the most complete information on isotopic kinetics. Unfortunately, these measurements are experimentally difficult with enzymatic reactions. An improved method for direct spectrophotometric comparison of β-galactosidase reaction rates obtained with natural abundance and highly enriched ^{18}O substrates has been reported.[37] In light of the reported precision, this method may become a viable alternative to the direct measurement of carbon isotope effects.

Competitive methods of measuring kinetic isotope effects have achieved greater precision but do not directly provide information on specific rate constants.[9,17,38,39] A general solution to this problem has been proposed through the mathematical comparison of $^{12}C/^{13}C$ and $^{12}C/^{14}C$ isotope effect data.[26] Similarly, the equilibrium perturbation method[40] has been developed for calculating isotope effects on the equilibrium and specific rate constants of reversible enzymic reactions.

A typical competitive study on an enzymatic reaction is carried out with an isotopic mixture of substrates (Eq. 2). Then the isotope effect

$$S_L + S_H \longrightarrow P_L + P_H \tag{2}$$

is calculated from the isotopic composition of products measured during the early reaction, and upon final completion of the reaction (Eq. 3).

$$(k_L/k_H)_{\text{measured}} = \frac{(P_H/P_L)\ 100\%\ \text{reaction}}{(P_H/P_L)\ \sim 5\%\ \text{reaction}} \tag{3}$$

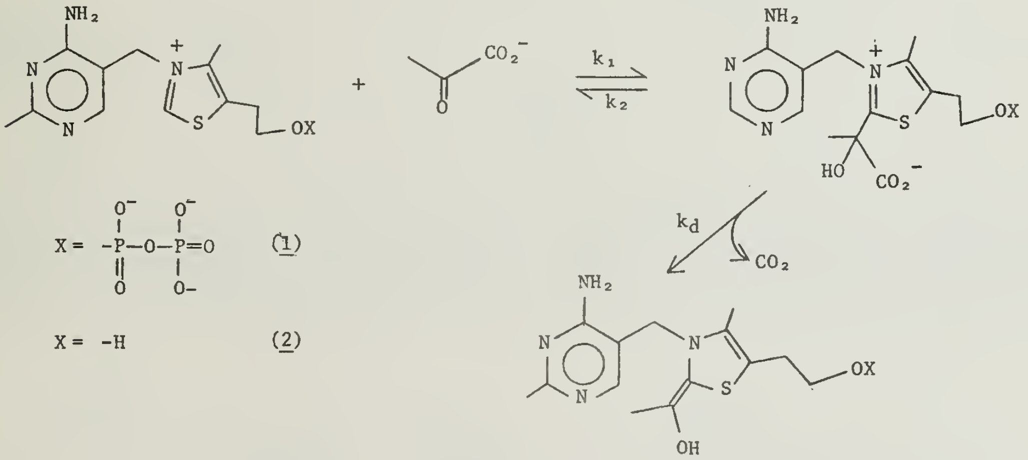
A correction can be made by extrapolating to 0% reaction.[41] When natural abundance ^{13}C substrates are used, the products must be isolated, totally combusted to CO_2, and analyzed with an isotope ratio mass spectrometer.[42] Of course, the results are only valid if there are no sources of isotope discrimination during sample handling and combustion. Despite the high detection sensitivity, liquid scintillation measurement of ^{14}C competitive reactions has not been widely used. Apparently, the concentration of radioisotope necessary to distinguish a kinetic isotope effect normally results in large counting errors from self-quenching in the sample.[9]

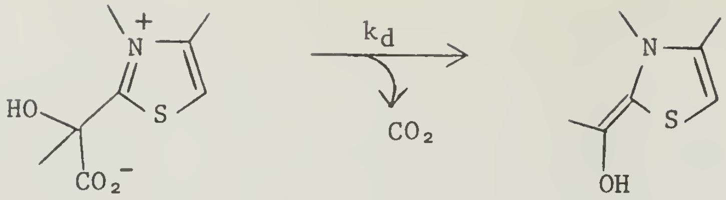
The use of direct probe mass spectrometry to measure isotope effects has been reported.[43] Recently, an improved method,[44] using repetitive scans, was demonstrated on the β-galactosidase reaction. Corrections for the fractional isotopic substitution (50% ^{18}O) were presumed to be least sensitive to any isotopic impurities. If applied to carbon isotope measurements, this method would facilitate the measurement of non-volatile products from synthetically enriched substrates. A novel double labeling procedure has also been introduced.[45] Methyl benzoate, isotopically labeled in two positions, was synthesized. The isotopic composition at one site was measured and then shown to reflect any isotope effect operating at the second (or reaction) site. The limitations of this method as a probe for enzymatic mechanisms would depend on synthetic efficiency or on the separation of singly labeled materials.

Recent Applications of Carbon Isotope Effects. Examples of carbon and other heavy atom isotope effects on enzyme catalyzed reactions have been reviewed.[4,9] Applications have ranged from predictions of substrate potential energy surfaces during enzymic catalysis[46] to in vivo assessment of competing metabolic pathways.[47] A combination of improved theoretical treatment and experimental measurement of isotope effects may prove to be a powerful method of studying enzymatic mechanisms. Recent investigations of carbon isotope effects illustrate new approaches in the analysis of enzymatic systems.

Jordan[48] has observed carbon isotope effects on the yeast pyruvate decarboxylase (PDC) reaction (Scheme I) catalyzed by thiamine pyrophosphate (1) and Mg(II). Thiamine (2) catalyzed decarboxylation of pyruvate (Scheme I) and decomposition of 2-(1-carboxy-1-hydroxyethyl)-3,4-dimethylthiazolium chloride (3, Eq. 4) were also investigated as model systems for the enzymatic decarboxylation step (k_d). On the basis of temperature and pH variations in the observed carbon isotope effects, an enzymatic mechanism was proposed in which k_d would be, at best, only partially rate limiting. Subsequently, the effect of solvent polarity on these model reactions was investigated.[49] The observed isotope effects were increased, suggesting relatively slower rates of decarboxylation in apolar media.

Scheme I



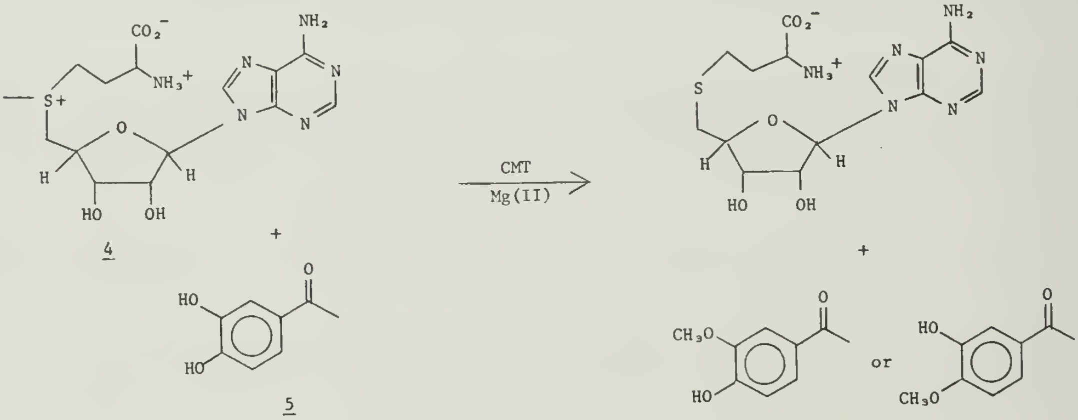


3

(4)

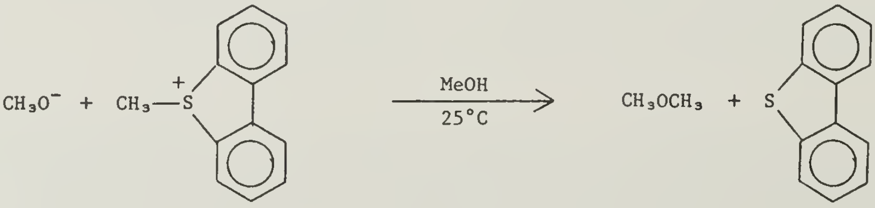
Further comparisons suggest that the existence of a hydrophobic PDC site can account for part of the enzymatic rate enhancement. Determination of the enzymic rate limiting step will require further investigations of model mechanisms.

Schowen[50-53] has studied the biologically important catechol O-methyltransferase enzyme (CMT), isolated from rat liver, by direct measurements of isotope effects. The enzyme catalyzes a methyl group transfer from S-adenosylmethionine (4) to a catechol (Eq. 5). Deuterium substitution in



(5)

the methyl group has indicated that methyl transfer is rate limiting and S_N2-like in the enzymatic mechanism.[50] Comparison of deuterium isotope effects on model systems provided evidence for a "compressed" geometry in the CMT active site.[51,54] A different model reaction was found (Eq. 6) to

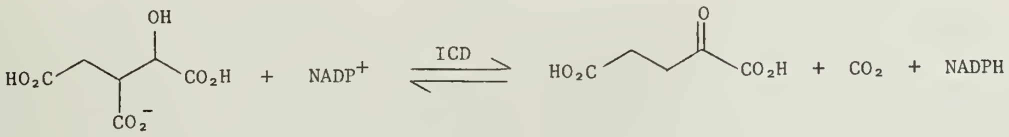


6

(6)

provide carbon and hydrogen isotope effects similar to those of the CMT system.[52] Both the model reaction and the enzyme were found to have carbon isotope effects larger than the maxima calculated from differences in S_o energies.[53] Although the two transition states may not be identical, the magnitude of the carbon isotope effect suggests a symmetrical structure for both enzyme and model.[55] Furthermore, isotope effects from synthetic analogues of 6 may illuminate the stereoelectronic requirements for this methyl transfer reaction.

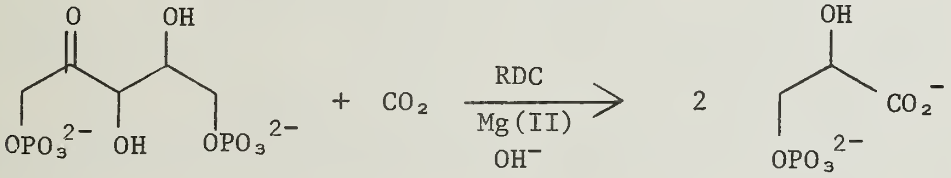
O'Leary[21] has demonstrated the precision of competitive methods by determining the equilibrium carbon isotope effect for the action of isocitrate dehydrogenase (ICD) on D-isocitric acid (Eq. 7). The enzymic



(7)

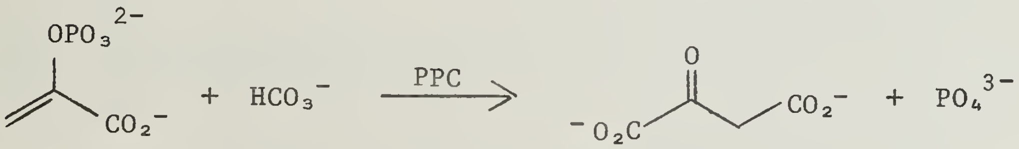
conversion is believed to occur via at least two steps[9] but all are apparently reversible. Identical equilibrium isotope effects were calculated for the reaction occurring in both a natural abundance $^{13}CO_2$ atmosphere and in one enriched in $^{13}CO_2$. The kinetic carbon isotope effect for ICD decarboxylation was determined previously.[56] Since the equilibrium isotope effect depends on the forward and reverse reaction rates,[4] the isotope effect for the reverse (or carboxylation) reaction can be predicted.

Plants incorporate CO_2 by similar photosynthetic carboxylation reactions. There is, however, a wide variation of observed carbon isotope content in different plants.[42,57] A rough division can be drawn between "C_3 plants", which rely mainly on ribulose diphosphate carboxylase action



(8)

(RDC, Eq. 8), and "C_4 plants", which can also fix CO_2 via phosphoenolpyruvate carboxylase (PPC, Eq. 9).[58] Carbon isotope content of plant



(9)

tissues, usually expressed as $\delta^{13}C$ values (Eq. 10),[59] is believed to reflect the relative activities of the two main carbon fixing enzymes.[60,61] In vitro experiments confirm different kinetic isotope effects for the two enzyme systems.[61-63] Whether these effects actually cause the isotope fractionation in plant tissues is not known.[64]

$$\delta^{13}C = \left[\frac{(^{13}C/^{12}C)_{sample}}{(^{13}C/^{12}C)_{standard^*}} - 1 \right] \times 1000 \qquad (10)$$

*primary limestone standard

Conclusions. Carbon isotope effects, if measured and interpreted carefully, are potentially powerful as tools in the study of enzymatic reactions. Kinetic and equilibrium isotope effects can characterize enzymatic mechanisms and transition state structures involving bond cleavage to carbon. Appropriate models and calculations can then serve to correlate observed isotope effects with the energy and structure of a proposed transition state.[21] It may even be possible to study the kinetics of ^{13}C-enriched biomolecules (such as enzymes and their cofactors)[34,65] in addition to labeled substrates. Further investigations of tissue isotope discrimination[48,66,67] may prove useful in obtaining in vivo information about metabolic crossroads. Finally, the use of multiple isotopic probes (e.g., C, H, O, N, S, and their common isotopes) should provide a technique for future rigorous studies of enzymatic mechanisms.

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RECENT THREE-CARBON ANNULATION METHODS FOR THE FORMATION OF CYCLOPENTENONES AND CYCLOPENTANONES

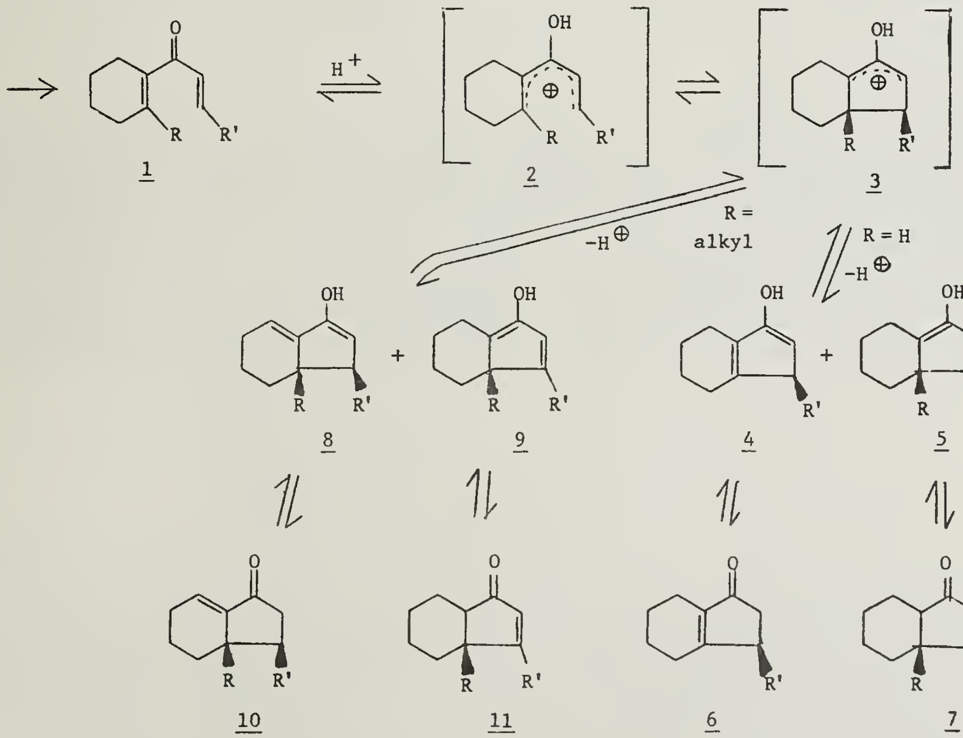
Reported by Pamela A. Albaugh March 24, 1980

In response to the widespread appearance of five-membered rings in naturally occurring compounds, investigators have directed much attention into the development of a simple and direct three-carbon annulation method. The simplest approach is to construct a five membered ring by the addition of a three-carbon unit to an appropriate two-carbon substrate. Typically the products of these annulation reactions possess functionalities which permit further synthetic elaboration.

Many of the three-carbon annulation methods of the early 1970's[1-5] suffer from either a lack of generality, poor stereoselectivity, or the use of harsh reaction conditions. New methods that circumvent these problems in the formation of annulated cyclopentanones and cyclopentenones is the subject of this report. There are three principle methods: the Nazarov cyclization reaction, the acetonyl cation synthon, and the formal [3 + 2] cyclization.

The Nazarov Cyclization. The Nazarov cyclization[6] is an electrocyclic ring closure of a cyclopentadienyl cation (Scheme I). These cations contain four π electrons and ring closure thus occurs by conrotatory motion in accordance with the Woodward-Hoffmann orbital symmetry rules.[7]

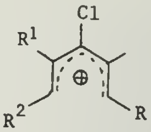
Scheme I



The position of the double bond in the final product reflects the stability of the cationic intermediates and a preference for the more-substituted double bond. Hence, the annulated cyclopentenones 6 and 10 are the preferred products.

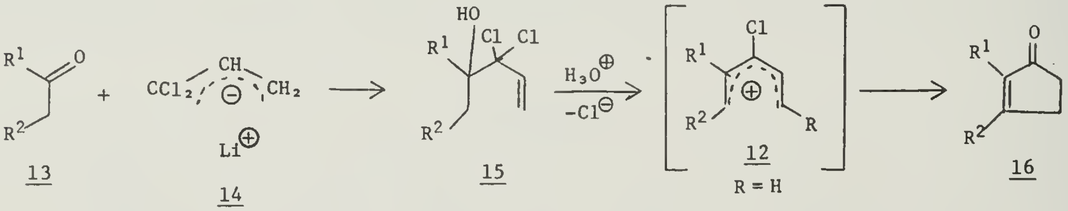
The dienone 1 is ordinarily formed in situ by a Rupe rearrangement of acetylenic diols[8] or by acylation of olefins with unsaturated acids in polyphosphoric acid.[9] The strong acid conditions required are not always compatible with other functional groups that may be present, e.g. ketals. Recently developed methodology permits preparation of the dienone, and/or cyclopentadienyl cation, under milder conditions.

Hiyama[10] extended the Nazarov method to analogous chloro-substituted cyclopentadienyl cations, 12. His initial observation[10a] that dichlorocyclopropyl carbinols are transformed to cyclopentenones upon treatment with acid, presumably through the cationic intermediate 12, suggested a more general method of cyclopentenone formation via the same intermediate. When a ketone is added to 1,1-dichloroallyllithium (Scheme 2),[10b] and then hydrolyzed, the cyclopentenone 16 is obtained generally in good yield. A variety of mild hydrolysis conditions can be used, including a Lewis acid.

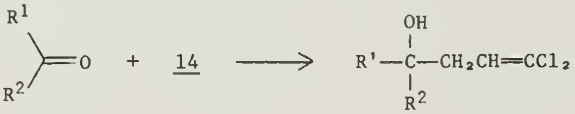


12

Scheme II



This approach has limitations. These are the lack of regioselectivity of the lithium reagent and the lack of regioselectivity of the cyclization. 1,1-Dichloroallyllithium is potentially an ambident nucleophile with the unsubstituted terminus being the "hard" end and the disubstituted terminus the "soft" end.[11] Hence, if the substrate ketone is made "hard" by having more polar character, then the desired attack by the disubstituted terminus becomes less favored and the undesired adduct 17 is obtained.

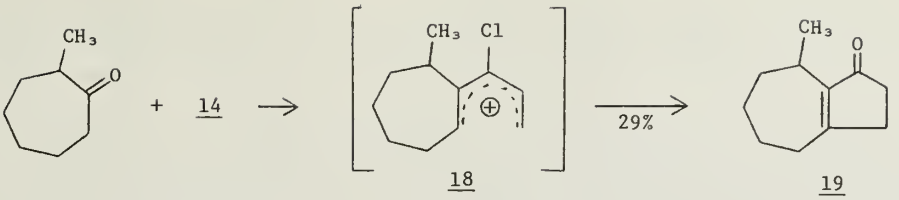


$$\mathrm{R'{-}\overset{\displaystyle OH}{\underset{\displaystyle R^2}{C}}{-}CH_2CH{=}CCl_2}$$

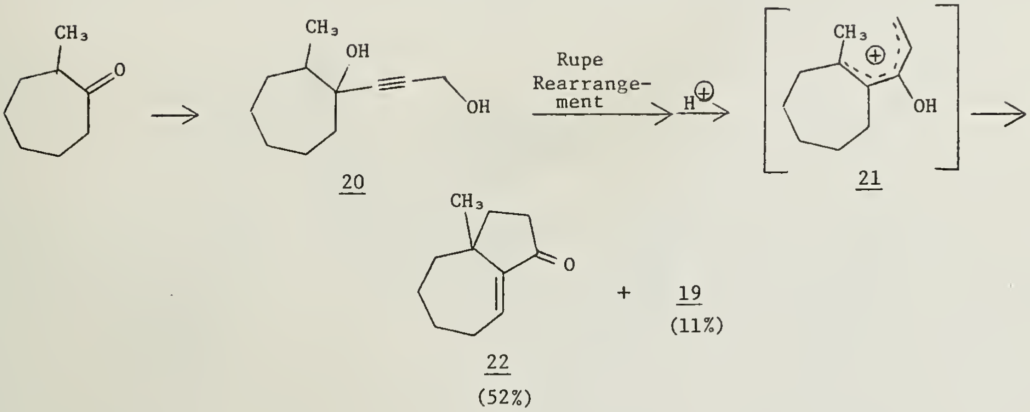
17

(1)

Steric factors also play a role. For example,[10b] when 2-methylcyclohexanone or 3-octanone are used, attack is solely from the unsubstitued end. In contrast, when 2-methylcycloheptanone is used, attack occurs from the disubstituted terminus, but cyclization forms the least substituted cyclopentadienyl cation, 18, rather than the more substituted 21 formed from acid-catalyzed hydration of the propargyl adduct 20.[8c]

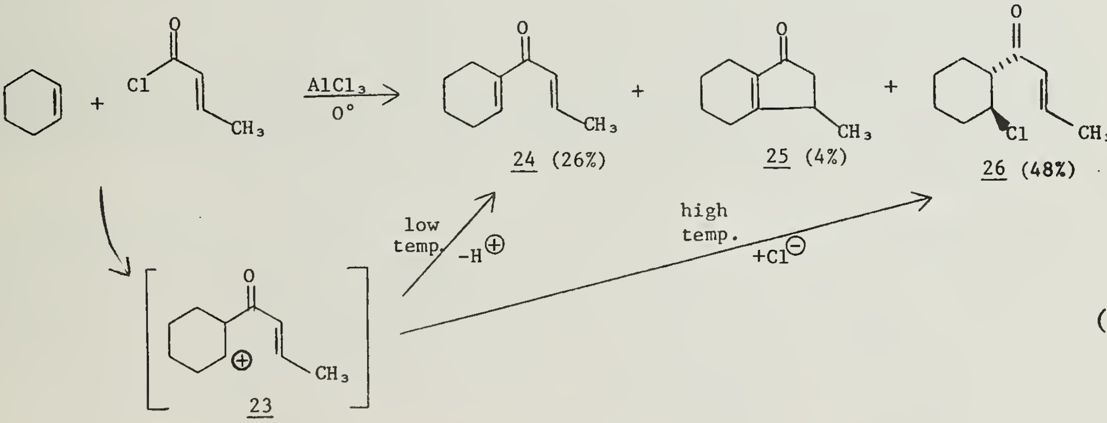


(2)



(3)

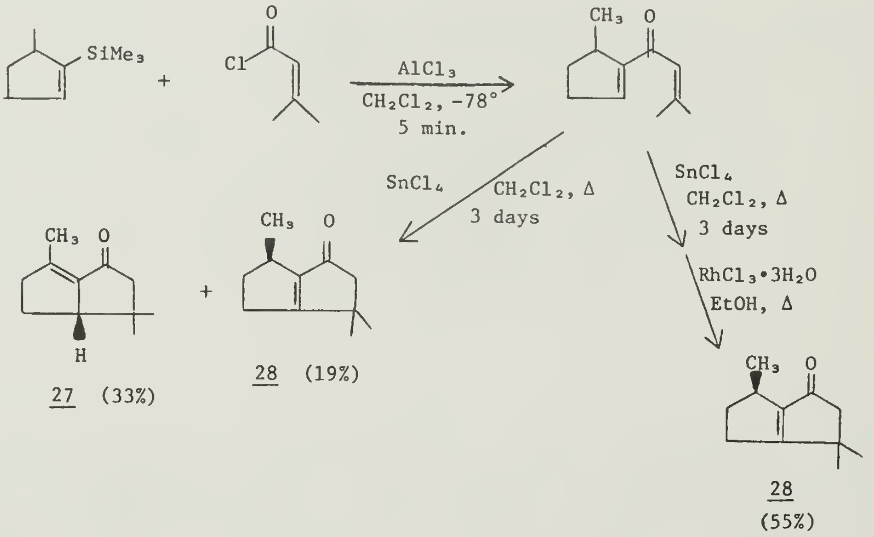
Recent extensions of the Friedel-Crafts acylation to afford ultimately cyclopentenones utilize Lewis acids in place of polyphosphoric acid. Acylating agents other than unsaturated carboxylic acids have also been used successfully. When crotonyl chloride reacts with cyclohexene in the presence of $AlCl_3$, a mixture of products (see Eq. 4) is obtained.[12]



(4)

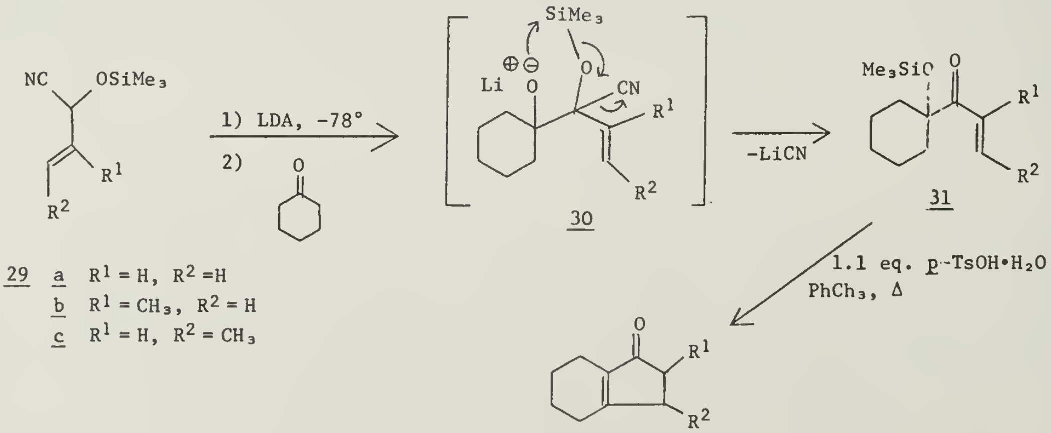
Santelli[12] postulated that the acylation proceeds through the cationic intermediate 23 which reacts further in a temperature-dependent manner to give 24, 25, and 26. When the more reactive crotonyl bromide reacts with cyclohexene at low temperature, none of the halo-adduct corresponding to 26 is isolated, and instead, a 72% yield of the annulated cyclopentenone is realized along with an 8% yield of the dienone. However, the generality of this reaction is limited because mixtures are obtained when substituted reactants are used. With the knowledge that dienones can be converted to cyclopentenones, Santelli demonstrated that the halo-adducts also serve as precursors to the cyclopentenones under acidic conditions.

Paquette[13] improved the Friedel-Crafts acylation by using a vinyl silane as the substrate olefin (see Eq. 5). The trialkyl silyl group directs the bonding of the acylium ion to the vinyl carbon bearing the silyl group as a result of its ability to stabilize a β-cation. The dienones need not be purified. Addition of $SnCl_4$ to complete the cyclization minimizes by-products containing chlorine or those resulting from methyl group migration. Treatment of the enone mixture before purification with $RhCl_3$ promotes isomerization to a single product.



(5)

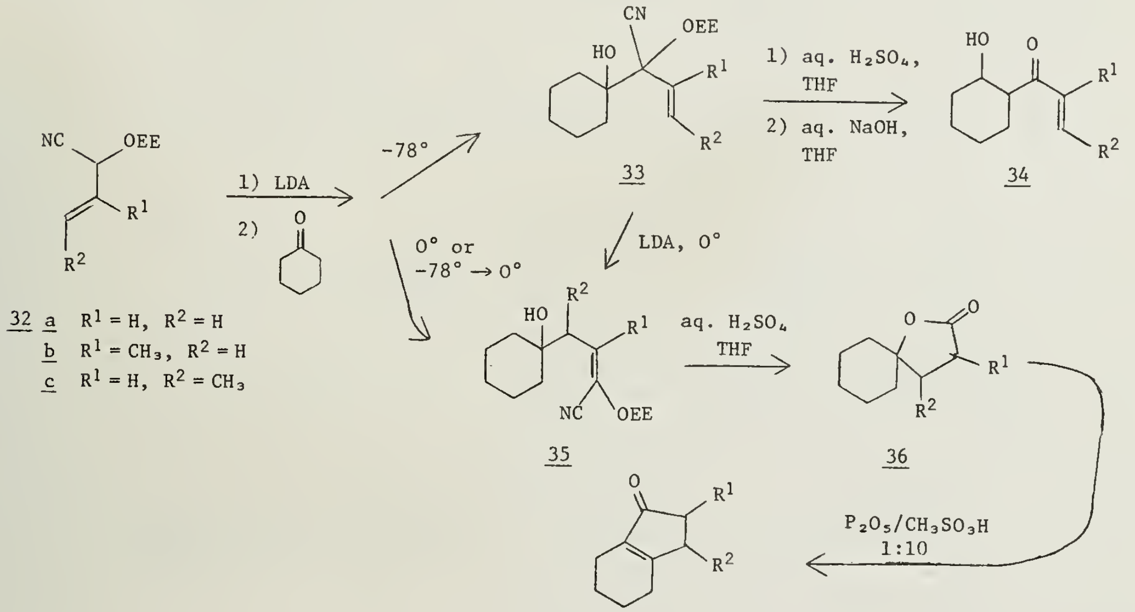
Another approach to the dienone is the reaction of an acyl anion equivalent with a ketone followed by dehydration. Jacobson[14] chose the anion derived from protected α,β-unsaturated aldehydes as the acyl anion equivalent. The anion of the trimethylsilyl-protected cyanohydrins (see Eq. 6) adds to ketones followed by intramolecular transfer of the silyl group and loss of lithium cyanide. Treatment with acid deprotects the alcohol and, upon dehydration, effects cyclization.



(6)

The anions of the ethoxyethyl-protected cyanohydrins (see Scheme III) also alkylate at the α-position at low temperature, but 32a and 32b alkylate at the γ-position at 0°C or when warmed to 0°C from -78°C. Reaction of 33 with lithium diisopropylamide at 0°C also gives the γ-alkylated adduct 35 which on hydrolysis gives the γ-lactones 36. These spirolactones can be converted to "inverted" cyclopentenones under acidic conditions.

Scheme III

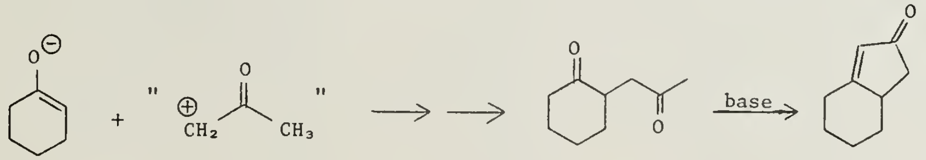


32 a $R^1 = H$, $R^2 = H$
b $R^1 = CH_3$, $R^2 = H$
c $R^1 = H$, $R^2 = CH_3$

In contrast, the ethoxyethyl-protected cyanohydrin 32c alkylates ketones at the α-position exclusively, even at 0°C. The trimethylsilyl-protected cyanohydrins decompose at 0°C.

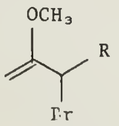
The α'-hydroxyenones 34 can be converted to the cyclopentenones by treatment with p-toluenesulfonic acid in good yield only when π conjugate stabilization is provided. Converting the α'-hydroxy enones, or the α'-trimethylsilyl enones, to α'-acetoxyenones eliminates by-products, giving the cyclopentenones in good yields upon treatment with p-toluenesulfonic acid.

Acetonyl Cation Synthon. Enolate alkylation of an acetonyl cation synthon and then, upon unmasking of the 1,4-dione, an internal aldol condensation to yield the annulated cyclopentenone (see Eq. 7) is the five-membered ring analogue to the Robinson annulation.



(7)

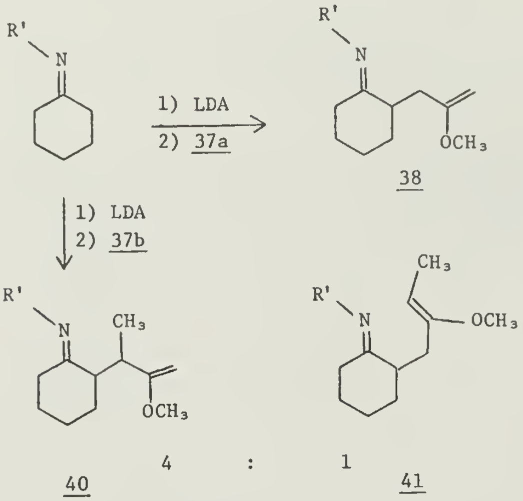
Recently, Jacobson used 2-methoxyallyl bromide[20] 37a and the homologue 3-bromo-2-methoxy-1-butene[21] 37b as the acetonyl cation synthon. Alkylation of imines, or other activated carbonyl compounds, proceeds in good yield (see Scheme IV) when 37a is used. A mixture resulting from S_N2 and $S_N'2$ attack is



37 a R = H
b R = CH_3

obtained from 37b. Conversion of 38 to the 1,4-dione, 39, is done cleanly with oxalic acid for most cases. Conversion of 40 and 41 to the corresponding 1,4-diones gives a complex product mixture of which furans and pyrroles are the major products. Optimum hydrolysis conditions still give a mixture of the desired diones as well as the furans. However, converting the furans to the diones with sulfuric acid gives a good overall yield of the dienone.

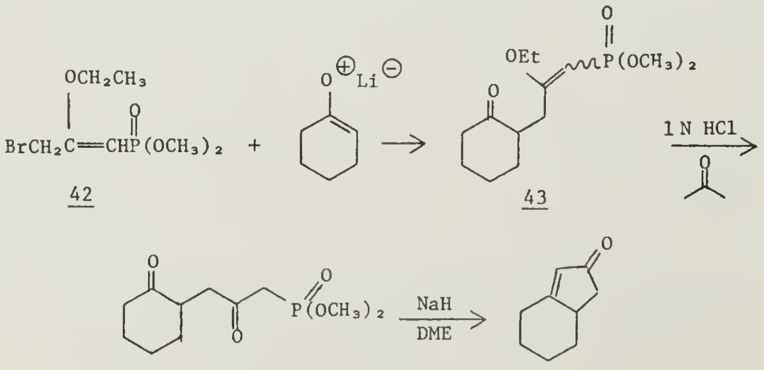
Scheme IV



The internal aldol condensation of the 1,4-dione to the annulated cyclopentenone can result in isomerized products.[4a,b,21] The isomerized products seem to result from the use of a protic solvent in conjunction with the base.

Piers[22] devised a method that essentially overcomes all of the aforementioned complications. Dimethyl 3-bromo-2-ethoxypropenylphosphonate, 42, formed in two steps in high yield from 2-oxo-propylphosphonate, reacts with the lithium enolate of a ketone to give the alkylated product 43 in quantitative yield (see Scheme V). Hydrolysis of the enol ether, followed by an internal Horner-Emmons reaction gives the annulated cyclopentenone in high yield. Ketals are left intact and no isomerized products are obtained.

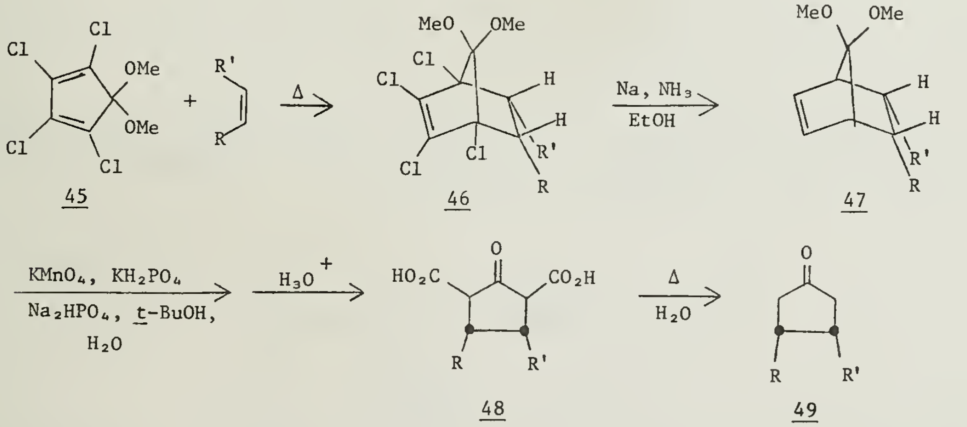
Scheme V



Formal [3 + 2] Cyclization. These transformations involve either several steps or non-concerted cyclizations since the cycloaddition of an allylic cation with an olefin is symmetry-forbidden thermally.

Performing a thermally symmetry-allowed operation, then cleavage of the extraneous portion (see Scheme VI),[23] is one approach to an overall [3 + 2] cyclization. A highly reactive diene was chosen to achieve reasonable yields with even the most unreactive olefins. The complicated buffer system for the oxidative cleavage gives optimum yields without by-products. When the olefinic substrate is ethyl vinyl ether, decarboxylation results also in elimination of ethanol. Hence, cyclic vinyl ethers possibly could yield annulated cylcopentenones.

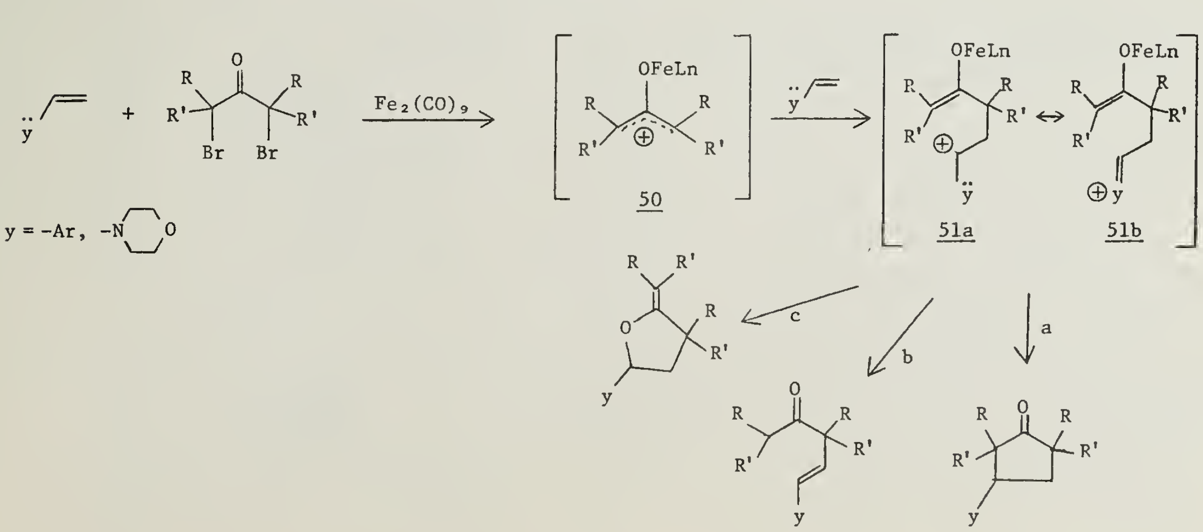
Scheme VI



One-step reactions that give annulated cyclopentanones are induced by transition metals and are postulated to go through a non-concerted cyclization even though it is known that the transition metals can, in theory, remove the symmetry restrictions and allow the cycloaddition to proceed thermally.[24]

Noyori[25] has reported the cyclization of α,α'-dibromo ketones with aromatic olefins and enamines. The reaction (see Scheme VII) is

Scheme VII

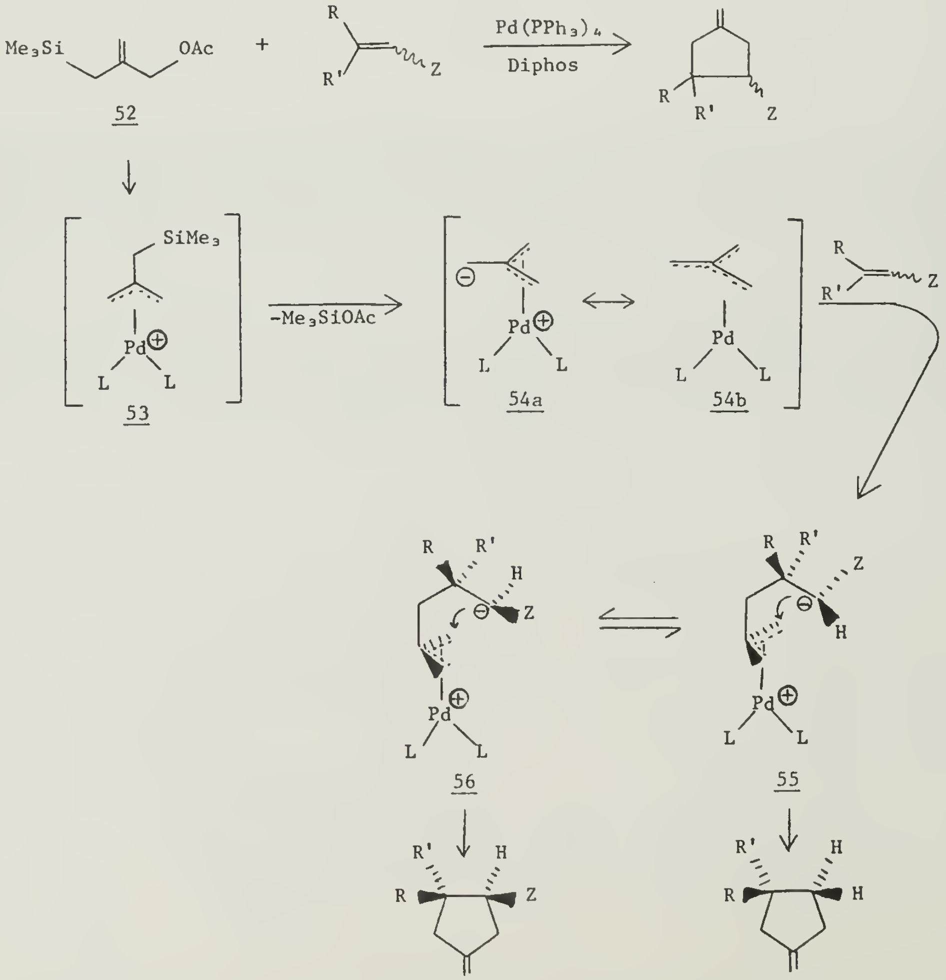


postulated to proceed through an oxyallyl-iron(II) intermediate, 50, which, upon attack on the olefinic substrate, generates the stabilized intermediate 51. Ring closure via path a produces the desired cyclopentanone in a stereospecific manner. Products derived from loss of a proton (path b) are formed in a non-stereospecific manner. Path c, cyclization on oxygen, is a competing reaction if there is steric crowding about the final ring-closing centers.

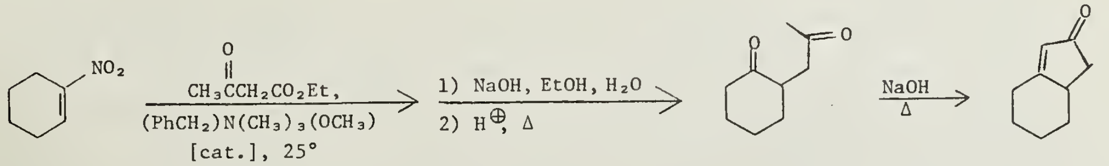
If an enamine is used as the olefinic substrate, deamination to the cyclopentenone often occurs during chromatography on silica gel or can be effected by 3% ethanolic sodium hydroxide. Overall yields are high, but diastereomeric mixtures are usually produced, when possible.

Trost[26] formed annulated methylenecyclopentanes via a palladium (0) catalyzed cyclization of electron-poor olefins with 2-acetoxymethyl-3-allyltrimethylsilane (see Scheme VIII). The reaction is postulated to proceed through a π-allylpalladium complex, 53, followed by a trimethylenemethane-palladium complex 54. Cyclization occurs in two steps since partial loss of stereochemistry is observed due to rotation about the free carbon-carbon bond before cyclization.

Scheme VIII

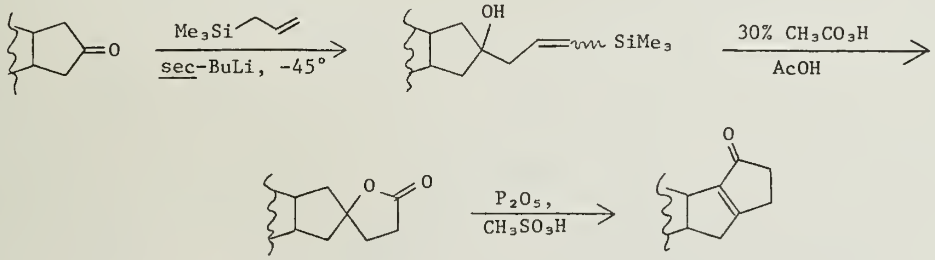


Miscellaneous. Not all reactions can be classified, as shown in Equations 8 and 9. The annulated cyclopentenone derived from a nitroolefin and ethylacetoacetate is produced in high overall yield.[27] The



(8)

annulated cyclopentenone derived from a ketone and the anion of allyltrimethylsilane is produced in good yield, but the sequence still employs undesirable conditions.[28]



(9)

Conclusion. A number of new three-carbon annulation techniques are now available to the organic chemist. Because of these numerous methods, the simplicity of the substrate, and the ease of accessiblity to an appropriate three-carbon unit, a wide variety of substituted cyclopentenones and cyclopentanones are now more readily approachable.

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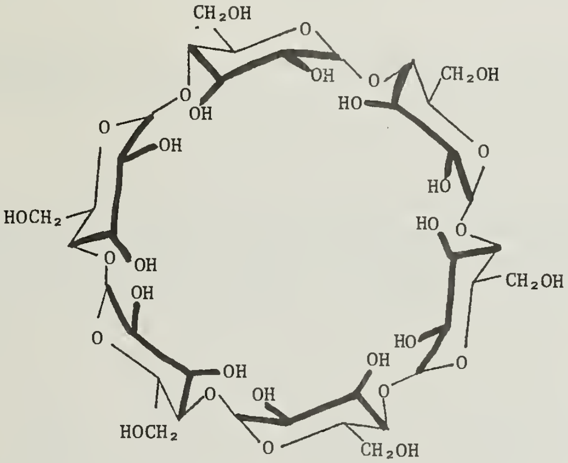
MODIFIED CYCLODEXTRINS AND THEIR USE AS ENZYME MODELS

Reported by Barbara Murray

March 27, 1980

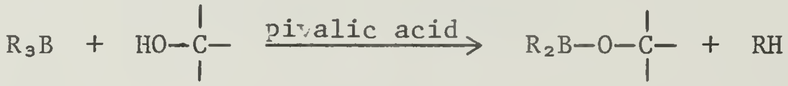
Cyclodextrins, also called Schardinger dextrins or cycloamyloses, are oligosaccharides produced by the amylase of Bacillus macerans on starches and similar compounds. Cyclodextrins are composed of α-(1,4)-linkages of several D(+)-glucopyranose units and are identified by a Greek letter to signify the number of glucose units: α- for 6, β- for 7, γ- for 8, etc.[1] The most common ones are α- and β-cyclodextrins, also called cyclohexaamylose and cycloheptaamylose. Examples with fewer than six glucose units have not been found. Cyclodextrins are doughnut-shaped structures with all the glucose units in chair conformations (Figure 1). The cavities are 4.5 Å (α-) to 7.0 Å (β-) in diameter and 6.7 Å (α-) to 7.0 Å (β-) deep with all the secondary hydroxyls (on C-2 and C-3) on one side and the primary hydroxyls (on C-6) on the other. The side with the secondary hydroxyls is slightly wider than the primary hydroxyl side. The interior of this cavity is thought to be relatively hydrophobic.[1]

Figure 1. Cyclohexaamylose



Cyclodextrins are known to form complexes with many compounds, especially compounds with aromatic components that fit into the hydrophobic pocket. Once the complexes are formed, cyclodextrins can catalyze the hydrolysis of esters or amides by the many hydroxyl groups around the edge of the pocket.[2] This region of the hydrophobic cavity and the secondary hydroxyls constitutes an active site similar to that postulated for enzymes.[3] Cyclodextrins' rates of hydrolysis of substrates can be compared with hydrolytic enzyme rates. But there are problems with using cyclodextrins as enzyme models: 1) they do not immobilize the bound substrate in a definite geometry thought necessary for great rate acceleration as an enzyme does;[4] 2) the observed binding constants are small compared to that of enzyme-substrate binding;[4] 3) cyclodextrins' maximum catalytic activity occurs at strong alkaline pH, while enzymes work around neutral pH;[5] 4) the rate of deacylation of the acylated cyclodextrins is less than the rate for direct hydrolysis of the ester;[5] and 5) the cyclodextrins are just too simple to serve as adequate models of complex enzymes.[5] The continuing interest in enzyme modeling has motivated many researchers to modify cyclodextrin rings with general bases or nucleophiles to solve some of the problems. There have recently been many successful modifications of the cyclodextrins which have proven to be interesting and informative as accurate enzyme models.

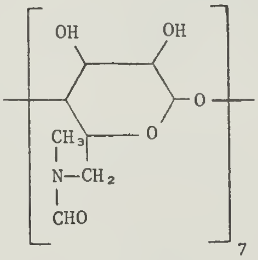
The modification of the ring structure is complicated by the large number of hydroxyl groups (18 for α-cyclodextrin and 21 for β-cyclodextrin) and by the difficulty in determining how many and which ones are being substituted. The first modifications consisted of forming various acetates, nitrates, and methyl ethers with little or no quantitative control.[6] The primary hydroxyls are usually the first to react. Umezawa and Tatsuta successfully tosylated all the primary hydroxyls in α-cyclodextrin (α-CD) by reacting it with 6-9 equivalents of p-toluenesulfonyl chloride in pyridine. Reaction of the tosylated α-CD with NaN_3 in DMF gives α-CD-N_3 in 52% yield. Reduction with hydrogen on Platinum oxide in methanol gives α-CD-NH_2 in 60% yield.[7] Cramer and co-workers made several derivatives from the tosylated α-CD, especially iodinated compounds.[8] Koster and co-workers borated the hydroxyl groups by using a trialkyl borane and pivalic acid as a catalyst (Eq. 1).[9] Recently, Lehn and co-workers have



$$R_3B + HO{-}\overset{|}{\underset{|}{C}}{-} \xrightarrow{\text{pivalic acid}} R_2B{-}O{-}\overset{|}{\underset{|}{C}}{-} + RH \qquad (1)$$

worked out synthetic routes for selectively modifying either the primary or secondary hydroxyl groups by using both steric control and the intrinsic functional reactivity of the hydroxyls.[10]

Most of the modifications have been done to more closely mimic the structure or reactivity of enzymes. Breslow and Emert synthesized 1 and 2 to form a "hydrophobic floor". They hoped that the "floor" would force the substrates into a fixed position and therefore would increase the rate of hydrolysis and the binding constants. With phenyl esters as substrates,



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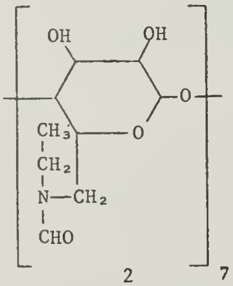

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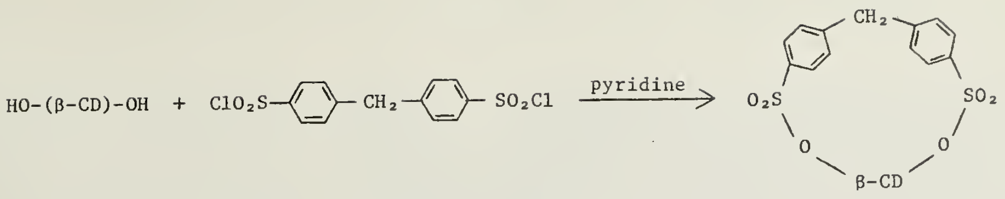
the rates do increase. For β-CD the rate is $k = 11.9 \times 10^{-3}$ sec^{-1}, while for 1 the rate is $k = 123. \times 10^{-3}$ sec^{-1} and for 2 $k = 210. \times 10^{-3}$ sec^{-1}. The "floor" did seem to put the substrate in a better position for the secondary hydroxyls to attack, but for some substrates the binding constants decreased because the cavity was now too shallow.[4,11]

Tabushi and co-workers synthesized a compound, 3, that many other workers have since utilized. They also reported using terephthaloyl



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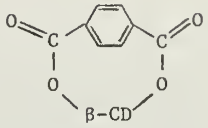
chloride to synthesize 4. They postulated that capping should strengthen the hydrophobic interactions and reported that 3 binds substrates 11-24 times more strongly than does β-CD.[12] In another study, they reacted 3 with various strong nucleophiles such as thiophenol to displace the cap and form compounds such as those shown below:[13]



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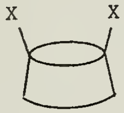


X = SPh, N_3, NH_2, or $SCH_2CH_2NH_2$

Fujita and co-workers found that the hydrolysis of phenyl acetates by 3 favors para whereas β-CD catalyzed hydrolysis favors meta. In the complex with 3, the para acetate group is closer to the hydroxyls while the opposite is true in the β-CD complex.[14]

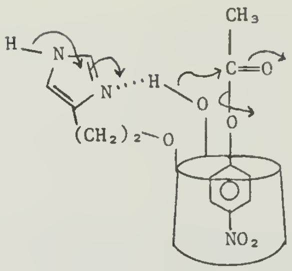
One of the enzymes for which modified cyclodextrins have been used as models is chymotrypsin. Chymotrypsin catalyzes the hydrolysis of peptides or esters. Both histidine and serine are present at the active site.[15] An acyl-enzyme intermediate is involved in the reaction for which this mechanism is proposed:

$$E + S \rightleftarrows ES \longrightarrow ES' + P_1 \longrightarrow E + P_2 \qquad (2)$$

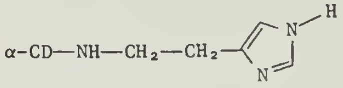
where ES is the enzyme-substrate complex and ES' is the acyl-enzyme intermediate.[16] Serine's hydroxyl group forms the acyl intermediate with the substrate while imidazole groups from histidines are also involved in the mechanism.[17] The interaction of the substrate with the enzyme surface rigidifies the whole set of bonds so that the carbonyl is in the correct position for reaction.[18]

One can easily see that cyclodextrins could serve as useful models for chymotrypsin by adding a group comparable to the histidines. In 1966, Cramer and Mackensen reported a hydroxymethylimidazole ether.[19] This compound has an average of two imidazole groups per cyclodextrin and accelerates the hydrolysis of p-nitrophenyl acetate (PNPA) 300 fold.[20] Cramer proposed that the mechanism worked as in Figure 2.[19]

Figure 2



Iwakura et al. synthesized 5. This model accelerates PNPA hydrolysis 60-80 times the α-CD rate and 5.5-6.3 times the rate of an α-CD-histamine mixture.[21] However, these figures are still much less than the chymotrypsin hydrolysis rate.



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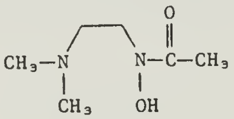
Another model for hydrolytic enzymes is based on the observation that N-(2-dimethylaminoethyl)acetohydroxamic acid, 6, catalyzes the hydrolysis of PNPA.[22] Bender and co-workers examined the nucleophilic hydroxamate groups in α-CD with 7, 8, and 9.[23,24] All three show a rate increase with 9 and 8 being the best. 8 also shows rapid deacylation which makes it closer to a true catalyst.[24]



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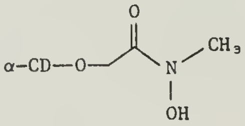

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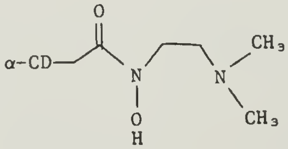

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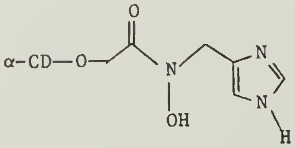


9

A closely related compound, 10, was made by van Hooidonk and co-workers. This compound, 10, has hydrolytic activity in neutral media.

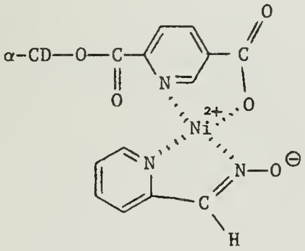
$CD{-}O{-}CH_2{-}CH{=}N{-}OH$

10

The oxime group makes 10 about 500 times faster than cyclodextrin towards PNPA.[3]

Another type of enzyme for which modified cyclodextrins have been used as models is the metal ion enzyme. A suspected role for the ions in the reactions is to hold the reactive groups on the enzyme and the substrate in the proper orientation to each other.[25] Breslow and co-workers have experimented with several different complexes, such as a zinc complex with pyridine-2-aldoxime[26] and a nickel complex with 2-cyano-1,10-phenanthroline.[27] These complexes do not have hydrophobic pockets, though, and so were not very good enzyme models.

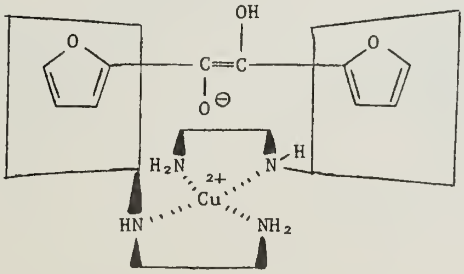
Cyclodextrins, with modified hydroxyl groups and their hydrophobic cavity, are potentially good models for metal ion enzymes. Using the knowledge gained from their previous work, Breslow and Overman prepared 11 using pyridine-carboxaldoxime (PCA). They found that 11 hydrolyzed PNPA in two steps: first, the PCA oxygen is acetylated and then a metal-catalyzed hydrolysis of the PCA acetate occurs. There was a 10^3 rate acceleration over the uncatalyzed rate, but not a great increase over a PCA-Ni^{2+} complex. Breslow concluded that still greater rigidity was needed in his catalyst to increase the rate further.[28]



11

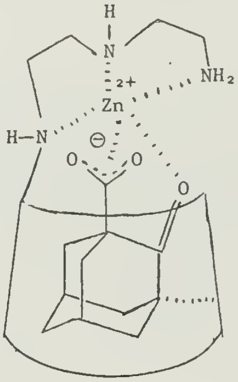
Matsui and co-workers examined a metal ion enzyme model. They made a 1:2 complex of Cu^{2+} with mono-(6-β-aminoethylamino-6-deoxy)-β-cyclodextrin and studied the oxidation of furoin to furil. The oxidation with the complex is 20 times faster than the uncatalyzed reaction. It is thought that the rate determining step may be the enolization process, and in the complex the enolate anion is stabilized electrostatically by the Cu^{2+} ion (Figure 3).[29]

Figure 3

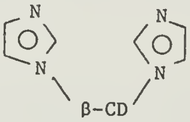


From the tosylated β-CD, Tabushi and co-workers made polyamine substituted cyclodextrins and complexed them with various metal ions such as Cu^{2+}, Zn^{2+}, and Mg^{2+}. The polyamine β-CD binds substrates 2-3 times better than β-CD, and the metal ion complex binds 330 times better. These complexes have both coulombic and/or coordination interactions and hydrophobic interactions (Figure 4).[30]

Figure 4



Tabushi also studied carbonic anhydrase, which has three imidazoles and a Zn^{2+} ion. Water, activated by Zn^{2+} coordination, attacks the CO_2 bound where the base catalysis by an imidazole may be involved. Tabushi and co-workers synthesized 12 and 13. These compounds, when Zn^{2+} is complexed with them, do catalyze the CO_2 ⟶ carbonate reaction but not at the rate that carbonic anhydrase does (Table 1). These rate differences do show that Zn^{2+}, imidazole, hydrophobic environment, and base are all involved in the enzyme catalyst.[31]



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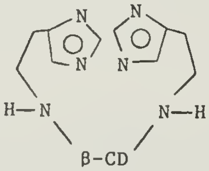


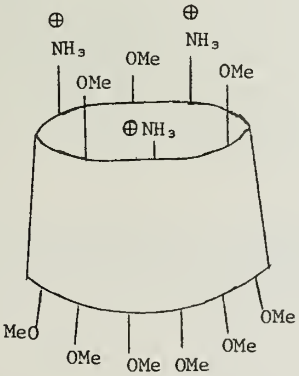
13

Table 1

Catalyst	Apparent k_{cat} (M^{-1} sec^{-1})
$(imidazole)_2Zn^{II}$	2.0
$(histiamine)_2Zn^{II}$	57.9
12 - Zn^{II}	16.2
13 - Zn^{II}	166.
carbonic anhydrase	10^7

Matsui and Okimoto synthesized (6-trimethylammonio-6-deoxy)-β-cyclodextrin hydrogen carbonate (14) which has a hydrophobic cavity and a cationic ammonium ion. They used an azo dye, sodium 4-(4-hydroxy-1-naphthylazo)-1-naphthalenesulfonate, as the substrate and compared binding constants at two pH's. At pH 4.0, where the hydroxyl group of the azo dye is undissociated, the ratio of binding constants, β-CD/14, is 0.66, while at pH 10.5, where the hydroxyl group is probably ionized, the ratio is 2.03.[32] Evidently, a charged group on β-CD does improve the binding of a substrate if the substrate also has a charge with which association can occur.

Boger and Knowles explored both hydrophobic and electrostatic interactions in a model for multiple recognition sites. They synthesized the triammonium compound 15 and used a phosphate monester, 16, as the substrate. Potentiometric titrations of 15 show that it is fully protonated at pH 7. The dissociation constants were measured for benzyl alcohol, $K_{diss} = 24.3$, and 16, $K_{diss} = 0.031$. The three cationic centers clearly hold 16, with its three partially anionic oxygens, much tighter than the neutral benzyl alcohol.[33,34]



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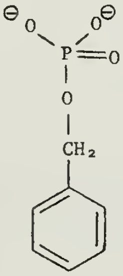
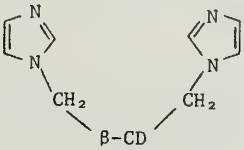


16

Breslow and co-workers prepared 17. The diimidazole should catalyze the hydrolysis of a cyclic phosphate substrate, such as 18, by a neutral imidazole, acting as a general base to deliver the water, and an imidazolium cation, acting as a proton donor.



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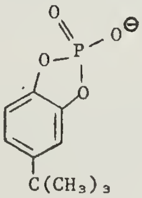

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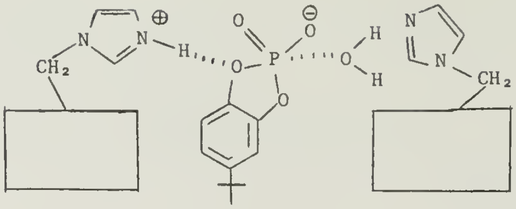
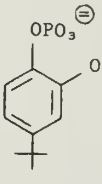
The substrate does not become covalently bonded to 17 (Figure 5).

Figure 5



One gets the same regioselectivity as with the enzyme, but the reaction is slower. In regular hydrolysis with $^{\ominus}$OH, one gets a 60:40 mixture of 19:20, but with both catalyzed reactions one sees only 20; thus, in both cases the substrate must be held tightly in a certain position.[35]



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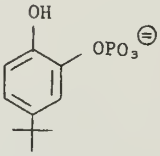
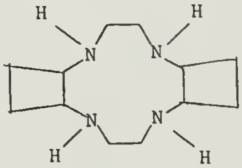


20

Tabushi and co-workers made "duplex cyclodextrin", 21, as a model for a triple recognition system. "Duplex cyclodextrin" binds methyl orange with



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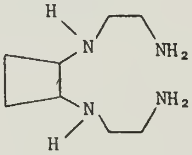
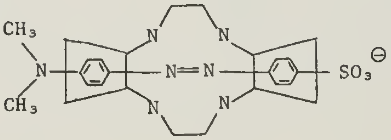


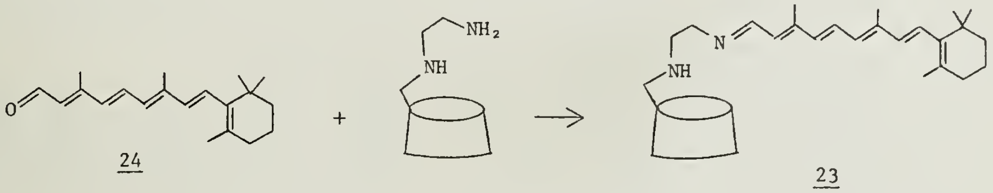
22

a higher binding constant than 22 due to the addition of the second hydrophobic site (Figure 6).[36]

Figure 6



Tabushi and co-workers have also synthesized 23 from retinal, 24 (Eq. 3). This compound shows a red shift in the electronic spectrum. Retinal bound to opsin comprises rhodopsin, the active pigment in the visual process in biological systems. This natural Schiff base causes a large red shift which has never been reproduced before under any comparable conditions. The Schiff base, 23, probably exists in a protonated form with the cyclohexene portion complexed inside the hydrophobic pocket.[37] Further work on this molecule may lead to valuable information applicable to visual pigment.



(3)

Breslow and co-workers have synthesized a cyclodextrin, 25, which acts like a transamination enzyme. With aromatic α-keto acids, 25 gives an amino acid ≈200 times faster than does simple pyridoxamine. The intermediate Schiff base is stabilized by inclusion of the aromatic portion in the cyclodextrin cavity (Figure 7).[38]

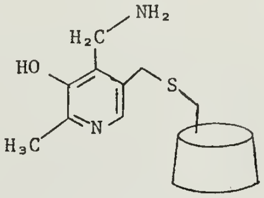


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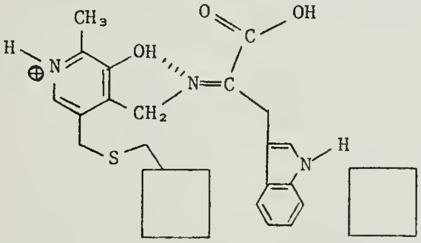
Figure 7



A final example of biomimetic models is a cyclodextrin-based ferredoxin model of $[Fe_4S_4(SR)_4]^{-2}$, where R = β-CD, synthesized by Siegel. He is presently studying the chemistry of one electron transfers between the iron-sulfur cluster and a substrate complexed with the cyclodextrin.[39]

One can see from these examples that modified cyclodextrins can be very useful as enzyme models. Scarce knowledge of enzyme structures can be used to construct new cyclodextrins. The knowledge learned from studying these compounds can then be used to further refine the enzyme's proposed structure and mechanism.

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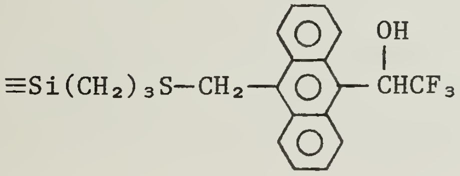
THE DIRECT RESOLUTION OF ENANTIOMERS BY LIQUID CHROMATOGRAPHY EMPLOYING A CHIRAL STATIONARY PHASE

Reported by John Finn April 7, 1980

The resolution of optical isomers continues to be one of the most troublesome problems in organic chemistry today. The idea of employing a chiral stationary phase to resolve racemates is as old as chromatography itself. The first attempts concentrated on using naturally occurring optically active substrates as the stationary phase. Buss and Vermeulen[1] have reviewed these attempts which are limited in scope. The rationale for chiral recognition was proposed by Ogston in 1948;[2] his hypothesis that a minimum of three points of interaction are necessary to distinguish enantiomers, is widely accepted and known as the three point rule.[3] In recent years a variety of rationally designed systems have been reported and are extensively reviewed.[4-6] These systems have had limited success as only one class of compounds, usually amino acids and their derivatives, are separated. Further, most systems have been only analytical in scale; the separation of preparatively useful amounts of racemates has been only rarely achieved.

In 1979 Pirkle and House reported the design of a chiral carbinol stationary phase, 1, which is capable of resolving racemic compounds containing a variety of functional groups.[7] The same rationale was used to design chiral amino acid-derived stationary phases which are capable of separating carbinols.[8,9] Of particular interest is the chiral stationary phase 2 which is capable of separating phenyl carbinols. A preparative scale column of 2 has been prepared and multigram resolutions are now routinely obtained.[10] The chiral carbinol system 1 has been modified and newer chiral stationary phases, 3, have shown marked improvements over 1.[9] In addition, a simpler and shorter synthetic route to chiral stationary phases 3 makes the production of a preparative column feasible.



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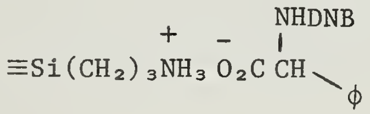

$\equiv Si(CH_2)_3\overset{+}{N}H_3\ \overset{-}{O_2C}\ \overset{NHDNB}{CH}\diagdown\phi$

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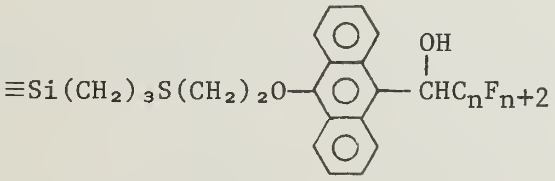

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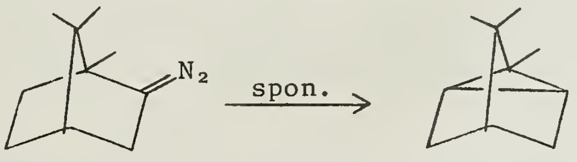
INTRAMOLECULAR CARBENE INSERTIONS: MECHANISM AND SYNTHETIC UTILITY

Reported by Larry Last April 10, 1980

One of the first reports of the intramolecular insertion of a carbene into a C-H bond appeared in 1930.[1] Heubaum and Noyes were attempting to measure the optical rotation of diazocamphane, 1, and discovered that it was only stable for a few days at -80°C. At higher temperatures, diazocamphane spontaneously decomposed to a non-olefinic compound identified as tricyclene.



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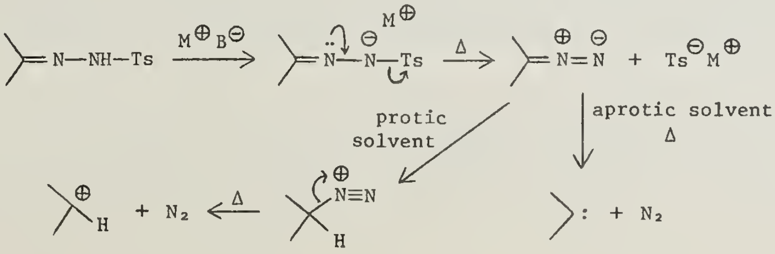
(1)

In the 1930's and 1940's, carbenes were generally regarded as diradicals. After the proposal by Skell and Woodworth[2] in 1956 that reactions such as Eq. 1 proceed through a triangular transition state, it became clear that carbenes are a unique type of intermediate, giving characteristic reactions not encountered with radicals. Since that time, the carbene literature has expanded rapidly and has been reviewed by Kirmse in 1964,[3] and again in 1971.[4] However, the synthetic utility of intramolecular carbene insertions has only recently begun to be appreciated.

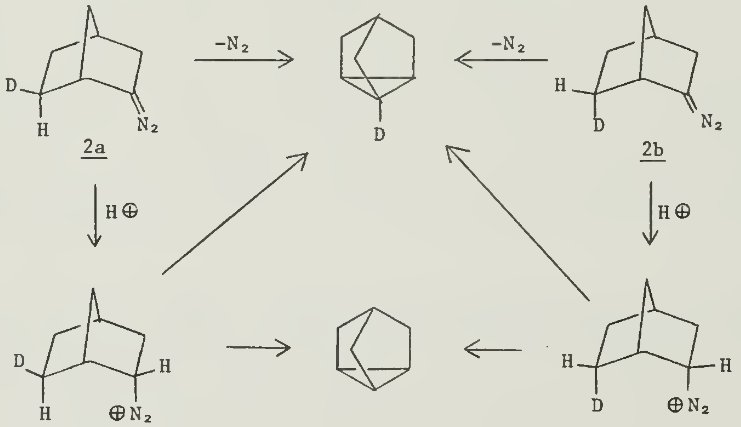
Methods of Formation of Carbenes. Numerous methods exist in the literature for the formation of carbenes, but only a few are of synthetic value in the realization of intramolecular insertion products. Of these, probably the most thoroughly studied is the Bamford-Stevens reaction,[5] or more correctly a modified Bamford-Stevens reaction.[6] Originally, Bamford and Stevens had identified the olefinic products recovered when a tosylhydrazone was heated with sodium metal in ethylene glycol.[5] The products were näively concluded to have arisen from a carbenic reaction. Subsequent studies by a number of workers indicate that there is actually a set of competing carbenic and cationic pathways being followed, with the former predominating in aprotic solvents and the latter in protic solvents.[7] Such a mechanism, which accounts for the product ratios in solvents of varying "protonicity", is outlined in Scheme I.

Scheme I



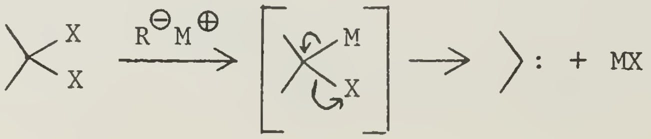
In 1962, Dauben and Willey[7a] observed that the photolytic decomposition of camphane tosylhydrazone resulted in a mixture of tricyclene and camphene, the ratio of which depends considerably upon the proton donating ability of the solvent. Although the trend toward increased tricyclene formation in solvents of decreasing "protonicity" is quite apparent, the issue is clouded by the fact that tricyclene could conceivably arise from a cationic process as well as a carbenic one. Evidence for the increase in the cationic mechanism in protic solvent was reported by Nikon and Werstiuk[7c] in 1966, when the tosylhydrazone precursors of 2a,b were heated with base under protic and aprotic conditions. As can be seen in Scheme II, any loss of deuterium in the nortricyclene product would confirm the presence of a cationic process. While there was no loss of deuterium label with diglyme as solvent, nortricyclene from 2a and 2b lost 19% and 52% of the label, respectively, when the reaction was run in ethylene glycol. Further studies[7d-g] confirmed the solvent dependence of the reaction mechanism.

Scheme II



It has also been observed that the identity and amount of base used in the decomposition of tosylhydrazones has an influence on the reaction mechanism.[7d,g,8] There is general agreement among workers that the use of 1.5 equivalents of sodium methoxide optimizes the yield of products derived from the carbenic process.

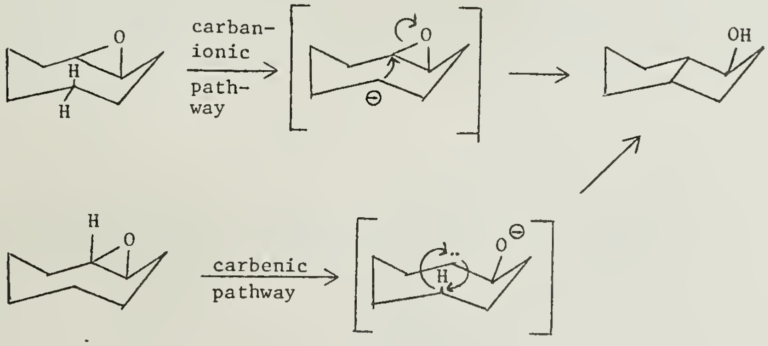
Probably second to the Bamford-Stevens reaction in frequency of use for generating carbenes is the metalation of gem-dihalo compounds. The reaction is believed to proceed as shown in Eq. 2. The most synthetically useful example of this mode of carbene formation involves the attack of an alkyl lithium reagent on a gem-dibromo compound.[9] Deuterium labeling provides evidence for the carbenic mechanism.[9]



(2)

In 1958, Cope and co-workers[10] observed that transannular insertion products resulted upon the heating of cyclic epoxides with lithium diethylamide. It was realized, however, that the products could be explained equally well by a carbanionic and carbenic process. These distinctly different mechanisms are presented in Scheme III for a representative cyclic epoxide. Cope confirmed the carbenic mechanism in 1966[11] by labeling the epoxide carbons with deuterium and observing the loss of half of the label in the bicyclic alcohol product. Crandall[12] and Boeckman[13] have added evidence for a carbenic process in other systems as well.

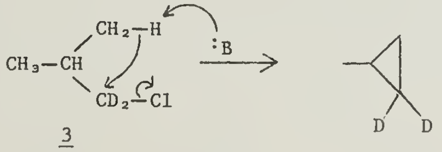
Scheme III



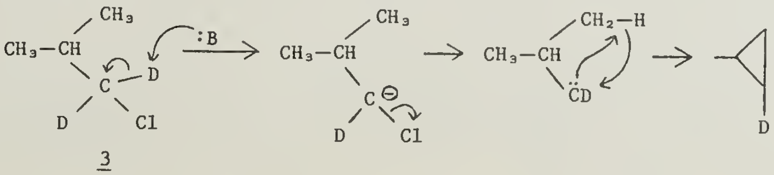
In 1941, Whitmore and co-workers[14] found that 1,1-dimethylcyclopropane resulted from the heating of neopentyl chloride with sodium metal in octane. The yield of cyclized product was later improved by employing propyl sodium as base.[15] The product was assumed to have been formed via an anionic mechanism, but it later became increasingly apparent that the results were better explained by an α-elimination mechanism, proceeding through a carbenic intermediate. Kirmse and Doering[16] provided the first solid evidence for a carbene mechanism in 1960 with their work on deuterated isobutyl chloride. As depicted in Scheme IV, γ-elimination

Scheme IV

γ-Elimination:



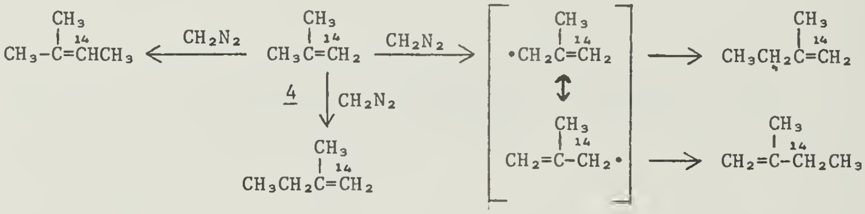
α-Elimination:



would be expected to result in dideuteriocyclopropane, whereas α-elimination would cause the loss of half of the deuterium label. When labeled chloride 3 is heated with sodium in cyclohexane, greater than 99% of the cyclopropane product is found to be monodeuterated. Further studies[17] with other appropriately deuterated molecules all come to the conclusion that the mechanism involves an α-elimination and subsequent carbene insertion.

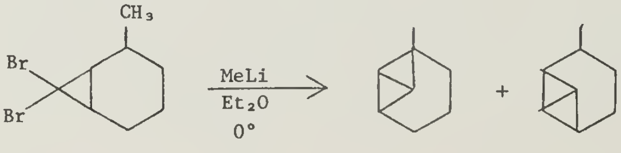
Mechanism for Insertion. In 1956, Skell and Woodworth[2] first suggested that the parent carbene, methylene, was planar, possessing sp^2 hybridization and a vacant p-orbital. They further proposed a triangular transition state for its insertion into C-H bonds. Diradical mechanisms were also considered,[18] but Doering and Prinzbach[19] provided convincing evidence for the triangular transition state model when they failed to detect isomerization when ^{14}C-labeled isobutene, 4, was photolyzed in the presence of diazomethane. Scheme V suggests that the existence of a diradical mechanism should give rise to some ^{14}C-3 labeled product.

Scheme V



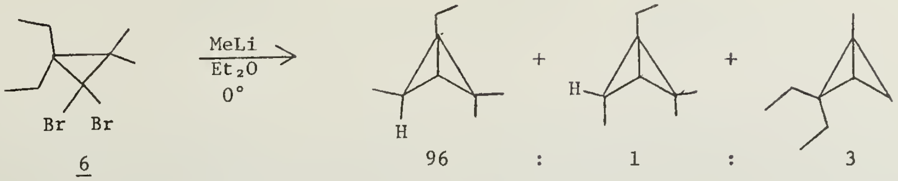
It was found that 99% of the original label was transferred to product without isomerization. Thus, the Doering-Skell triangular transition state model for carbene insertion has become generally accepted.

Selectivity of Carbene Insertions. Gutsche and co-workers[20] conducted the first comprehensive study of the inherent reactivity of C-H bonds toward carbene insertion. They confirmed the generally accepted idea that tertiary C-H bonds are more reactive toward carbene insertion than secondary, which are both more reactive than primary, all other factors being equal. Other workers[21] have arrived at the same conclusions. In fact, Reinarz and Fonken[21c] found that treatment of 7,7-dibromo-2-methylnorcarane, 5, with methyl lithium in ether results in tertiary C-H insertion to the exclusion of insertion into the secondary C-H bond, as shown in Eq. 3.



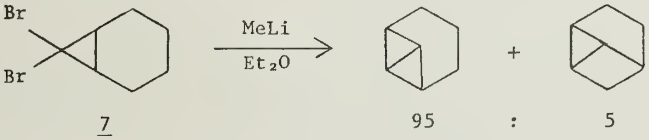
5 1 : 0 (3)

Similar results were obtained with the dibromocarbene adduct of pulegene. Moore and Hill[21a] demonstrated the enhanced reactivity of secondary over primary C-H bonds toward carbene insertion when 1,1-dibromo-2,2-diethyl-3,3-dimethylcyclopropane, 6, is treated with methyllithium in ether. As shown in Eq. 4, a strong preference for methylene over methyl C-H insertion is observed.



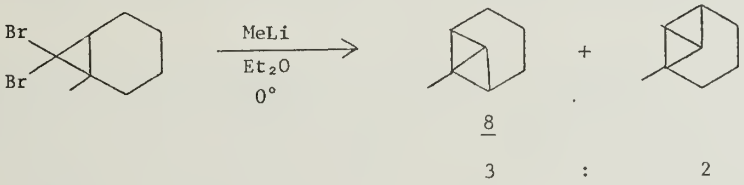
(4)

Probably the most influential factor in determining the selectivity of intramolecular carbene insertions is the proxmimity of the carbenic carbon to potential sites of attack. Stated simply, the closer a C-H bond is to the developing carbene center, the more likely it is to be attacked. This simple idea was first demonstrated by Moore and co-workers[22] when 7,7-dibromonorcarane, 7, was treated with methyl lithium. They found that the bicyclobutane product formed in great preference to the bicyclopentane product (Eq. 5).



(5)

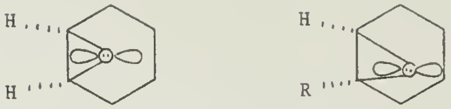
Paquette and Taylor[23] have extensively studied the proximity effects on carbene insertion in the alkyl-substituted dibromonorcarane system. It was found[23] that a methyl substituent at C-1 creates a preference for insertion into the C-H bond adjacent to the point of substitution (Eq. 6).



(6)

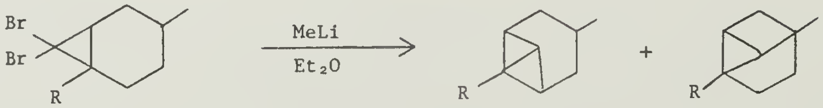
Cory and co-workers[24] have confirmed this ratio. In the case of the analagous norcar-3-ene, the ratio increases to 3:1.[23a] When the alkyl substituent is isopropyl or t-butyl, only the isomer analagous to 8 is observed.[25]

It was suggested that these and similar results[26] arise from subtle proximity effects.[23b] Thus, alkyl substitution at the bridgehead position causes twisting of the cyclohexane ring in order to minimize nonbonded interactions. Such a change in conformation of the ring causes the incipient carbene center to be drawn closer to the C-H bond adjacent to the point of substitution (9). This decreased distance results in a preference for attack.



9

In the case of dibromide 10a, the ratio of tricyclic 11a and 12a is 2.3:1. With a methyl substituent (10b), this ratio increases to 8.3:1 (Eq. 7).[25]

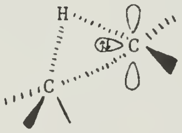


(7)

	10	11		12
a:	$R = H$	2.3	:	1
b:	$R = CH_3$	8.3	:	1

Other substitution patterns confirm the preference for attack at the site presumably favored by proximity effects.[23b]

The regioselectivity of transannular carbene insertions is believed to be a result of two contributing factors: proximity effects and orbital orientation. In 1975, Casanova and Waegell[27] considered three distinct orientations of the carbene center in the triangular transition state model, 13-15, and concluded that the results of previous studies were best explained by 13, in which the empty p-orbital of the carbene carbon is, or is nearly, parallel to the C-H bond under attack. Employing this model for the transition state geometry and Dales's[28] models for the lowest energy configuration of medium rings, the regioselectivity of insertion observed in numerous studies[29] is explained quite well.



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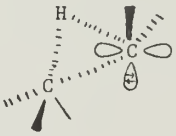

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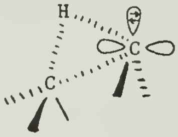
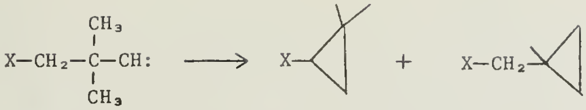


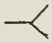
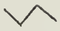
15

A final factor to be considered in the selectivity of intramolecular carbene insertions is that of substituent effects. Little work has been conducted in this area, but Kirmse and co-workers[30] have found that electron withdrawing substituents cause a definite decrease in the reactivity of an adjacent C-H bond. As seen in Table 1, the rate of reaction at a C-H bond in carbene 16 steadily decreases as the electron withdrawing power of X is increased.

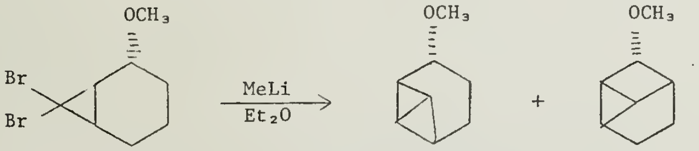
Table 1



16

X				CH_3	Ph	$CH{=}CH_2$	$N(CH_3)_2$	OCH_3
Rate of 2°/1° insertion	0.95	0.95	0.85	0.78	0.50	0.43	0.21	0.06

Paquette and co-workers[31] have found analagous deactivation in a series of methoxyl-substituted norcaranes. An interesting result of this study is the finding that the methoxyl substituent actually appears to assist in the insertion into a C-H$_{\beta}$ bond. This assistance is best exemplified by the products in Eq. 8 when compared to those in Eq. 3.



23 : 77 (8)

The enhanced C-H$_{\beta}$ reactivity is attributed to "backside" assistance provided by the axial methoxyl substituent. The developing epioxonium characteristics by trans diaxial involvement of methoxyl oxygen could reasonably increase the normal levels of C-H$_{\beta}$ nucleophilicity. Carbenes in which the methoxyl group is equatorial and unable to participate in this manner exhibit little or no propensity for C-H$_{\beta}$ insertion.[31]

Novel and Efficient Uses in Synthesis.* Intramolecular carbene insertion reactions have been used to accomplish a wide variety of synthetic transformations. The undaunted interest in the synthesis of strained molecules has prompted workers to exploit the ring-formation potential of transannular insertions. Udding and co-workers[32] have elaborated the adamantane skeleton in the efficient synthesis of tetracyclo[3.3.1.^{3,7}0^{2,4}]decane, while Geluk and deBoer[33] accomplished a double carbene insertion in the synthesis of pentacyclic 17. Baird and co-workers[34] take advantage of the favorable geometry in the pinane skeleton to synthesize tetracyclic 18 in yields in excess of 90%. Pseudopelletierine[35a] and related compounds[35b,c] are converted to 19 in reactions in which the yields of olefinic products have been minimized.

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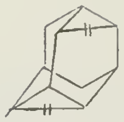
*In order to more easily visualize the insertion reaction, structures have been drawn with slashes through the bond(s) being formed.



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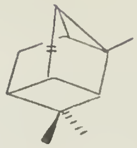

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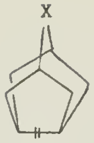
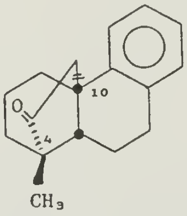


19

$X = NCH_3$, CH_2, S

One of the key problems in the total synthesis of a large number of complex diterpenoids, for example the *Garrya* and *Atisine* groups of diterpene alkaloids, is the introduction of the C-10 functionalized carbon residue in combination with the C-4 substituent with appropriate stereochemical control in a hydrophenanthrene or hydrofluorene moiety. Ghatak and Chakrabarty[36] accomplished this with a surprisingly efficient intramolecular insertion into the C_{10}-H bond to produce ketone 20, which is conveniently converted to a key intermediate in the total synthesis of racemic atisine,[37] veatchine,[38] and gibberellin-A_{15}[39] by Nagata and co-workers.



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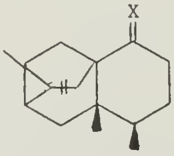

21 a: $X = H_2$
b: $X = O$

Cory and co-workers have employed an ingenious method of simultaneously utilizing two characteristic reactions of carbenes: addition to a multiple bond, followed by *in situ* metalation and subsequent carbene insertion into a C-H bond, in the total synthesis of ishwarane,[40] 21a, and ishwarone,[41] 21b. Intramolecular carbene insertions have also been used in the synthesis of indols,[42] indolines,[43] indans,[44] steroids,[45] penicillins,[46] carbapenems,[47] and a wide variety of other examples. In most cases, the insertions are highly regioselective and efficient, and often reduce the number of steps in a synthetic transformation dramatically.

Conclusion. The intramolecular carbene insertion reaction is a very useful weapon in the arsenal of the synthetic chemist because of its reliable dependence on proximity effects and bond nucleophilicities. As a result of the concertedness of the insertion, retention of configuration is virtually always attained, allowing for strict stereochemical control when desired. These characteristics, coupled with the good yields obtainable in most insertion reactions, should result in their increasingly more frequent use in synthesis.

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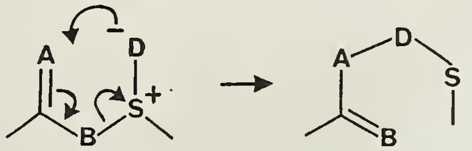
[2,3] SIGMATROPIC REARRANGEMENTS OF SULFONIUM YLIDES

Reported by Scott W. Landvatter April 14, 1980

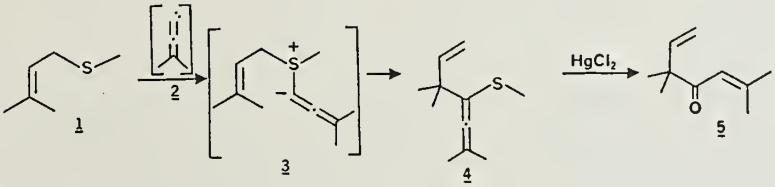
Alkylsulfonium alkylides undergo a thermal, symmetry allowed, [2,3] sigmatropic rearrangement to produce homoallylic sulfides. In the general case, A, B and D need not be carbon.[1] The analogous rearrangement has



been observed with nitrogen ylides,[2] allylic ethers,[3] and various other systems.[4] The all carbon system has also been studied.[5] After a brief look at the general aspects of this reaction, this review will focus on two new developments in the synthetic utility of this rearrangement: multicarbon ring expansion and the specific ortho substitution of anilines and phenols.

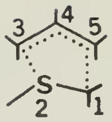
Only in the past ten years have the numerous synthetic possibilities of this reaction, as applied to sulfonium ylides, been exploited. It has been used in various natural product syntheses, including squalene,[6] yomogi alcohol,[7] and E-nuciferol.[8] Yoshimoto[9] has also employed the rearrangement in the conversion of cephalosporins to penicillins.

The most recent application has been in the synthesis of the naturally occurring monoterpene, artemisia ketone.[10] One of these syntheses uniquely employs an allenic sulfur ylide. This synthesis typifies the general procedure for carrying out the rearrangement. Allylic sulfide, 1, when treated with allenic carbene, 2 (generated from 3-chloro-3-methyl-1-butyne and methyl lithium), produces an intermediate ylide which rearranges on warming from -78° to room temperature to give an allenic thioether, 4. Hydrolysis by mercuric chloride gives artemisia ketone, 5, in 30% overall yield.

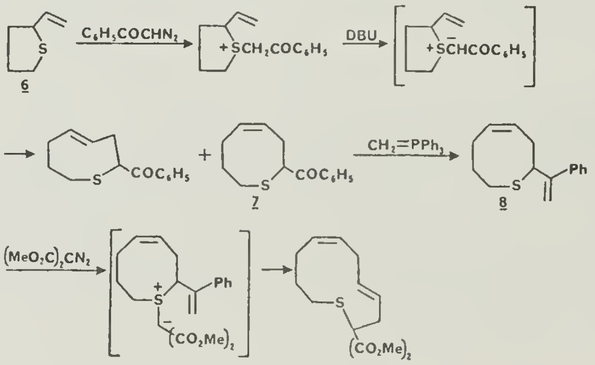


In cases where 1,2-disubstituted olefins are produced, the preferred stereochemistry about the double bond is the E geometry. Greico,[11] for example, has observed that the rearrangement of α-substituted methallylsulfonium ylides results in a 9:1 mixture of E and Z olefins, respectively. Similar results have been obtained with sulfoxides.[12] In fact, the E isomer accounts for 80-98% of product in nearly all cases involving [2,3] sigmatropic rearrangement of acyclic sulfonium ylides.[13]

The folded envelope conformation nicely accommodates preferential formation of a trans double bond. Analysis of this conformation leads to the conclusion that a bulky group introduced at C_3 should adopt a pseudo-equatorial position. The product of rearrangement from this conformation would have the bulky group *trans* to the thioether unit, while placement of the bulky group in the sterically constrained pseudo-axial position would lead to *cis* olefin formation. Similar analysis indicates that a bulky group at C_1 prefers an *exo* orientation.[7,15-17]



Ring Expansion. Several methods are available for multicarbon ring expansions, including fragmentation of a bicyclic intermediate derived from a monocyclic precursor,[18,19] or central bond cleavage in a bicyclic transition state.[18,20] However, each of these suffers the disadvantage of being non-repeatable. Through a series of [2,3] sigmatropic shifts, on the other hand, an easily repeatable "ring growing" sequence allows systematic ring enlargement. In the first step an α-vinyl heterocycle, such as 2-vinyltetrahydrothiophene (6), is converted to a sulfonium salt. Treatment with 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU), or a variety of other bases, generates a sulfonium ylide which rearranges to produce a mixture of ring expansion products, the major isomer (67%) being the *cis*-thiacyclooctene (7). This can be further expanded by treatment with methylidenetriphenylphosphorane (Wittig reaction) to afford a new α-vinyl heterocycle (8). Treatment with dimethyl diazomalonate produces a new stabilized ylide which rearranges to give only one isomer of an 11-membered heterocycle.[21]

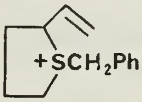
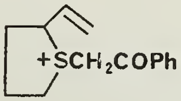
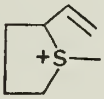
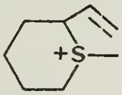
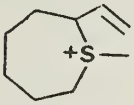


The great synthetic utility of this reaction has recently been demonstrated by Schmid.[23] Starting from 2-vinyltetrahydrothiophene, a 17-membered heterocycle was produced in 49% overall yield via repeated addition of allyl bromide and potassium hydroxide. This procedure is a distinct improvement over the method of Vedejs in that the reaction can be carried out without isolation of any intermediates.

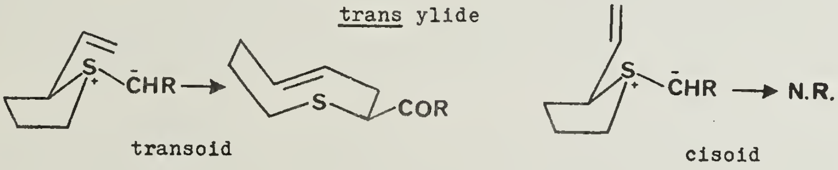
Several methods are available for the formation of the initial sulfonium salt and ylide. Copper-bronze catalyzed decomposition of a diazocarbonyl compound, conditions which promote carbene generation, in the presence of a sulfide, produce the sulfonium ylide directly.[21,24] Excellent results have also been obtained by heteroatom alkylation with trifluoromethanesulfonate esters (triflates). Allyl triflate and the triflate derived from ethyl glycolate have been used.[24] The salts which are produced in these alkylations occur by least hindered approach of the alkylating agent, thus producing a *trans* sulfonium salt, *i.e.* the alkyl group is *trans* to the vinyl group.[21,22,24,25] *In situ* generation of the sulfonium ylide by addition of bases gives ring expanded products.

Mechanistically, this reaction poses some interesting questions. Table 1 summarizes product stereochemistry in the ring expansion of 5, 6 and 7-membered heterocycles. In all cases, ring expansion of 5-membered 2-vinyl heterocycles produces a *cis*-thiacyclooctene as the major isomer.

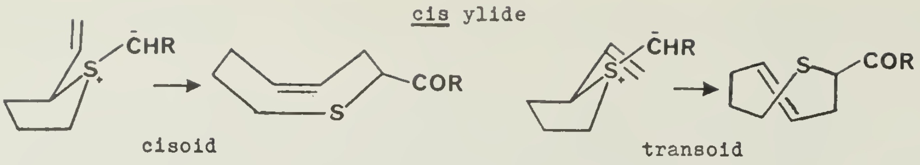
Table I

Starting Salt	Product Stereochemistry (*trans*:*cis* ratio)
	.08
	.10
	.17
	24
	50

Expansions of larger rings show just the opposite trend. Examination of ylide conformation does not provide an easy answer. Two conformations are possible for the ylide obtained from the *trans* sulfonium salt, a cisoid and a transoid conformation.[21,24] Of these, only the transoid can obtain a reasonable geometry for reaction to occur. The cisoid vinyl rotamer cannot achieve the necessary orbital overlap to permit rearrangement. However, the transoid conformer gives only the minor product, *trans*-thiacyclooctene (7% of product).



To explain preferential formation of the *cis* isomer it is necessary to equilibrate the *trans* ylide with the *cis* ylide. In this case the cisoid vinyl rotamer will produce the observed major product, while the transoid rotamer gives the *trans* heterocycle. Three possible routes exist for this *trans* to *cis* interconversion,[24] pyramidal inversion at sulfur,



fragmentation of the allylic C-S bond and reclosure, and reversible deprotonation-protonation α to the vinyl group. Fava[27] has noted that pyramidal inversion at sulfur should be slow in cyclic systems for steric reasons, while stabilized ylides invert slowly at 25°.[24] Furthermore, since the majority of rearrangements occur at temperatures less than 0°, sulfur inversion should be insignificant. Fragmentation of the allylic C-S bond, followed by reclosure, would be expected also to form a 6-membered ring, but this is not observed.[24]

Several systems have allowed testing of the viability of reversible proton abstraction. Fava[26] treated *trans*-1-methyl-2-vinyltetrahydrothiophene with a 50% defect of base. Quenching with D_2O and recovery of excess sulfonium salt showed a 1:1 mixture of *cis* and *trans* sulfonium salts with deuterium incorporation at C_2. Therefore, in the case of non-stabilized sulfonium ylides, ring expansion does not compete favorably with proton abstraction, resulting in sulfonium salt isomerization. Unfortunately, this says nothing of the relation between the stereochemistry of the starting sulfonium salt and product. In order to preclude this isomerization pathway, Fava[28] replaced the acidic C_2 hydrogen with a methyl group in both 1-methyl-2-vinyltetrahydrothiophene and 1-methyl-2-vinyltetrahydrothiopyran. Due to difficulty in isomer separation, *cis* and *trans* mixtures of sulfonium salts were subjected to ring expansion conditions with variable defects of base and the product distribution examined.

When a 7:3 mixture of *cis* and *trans*-1,2-dimethyl-2-vinyltetrahydrothiophene (*i.e.* methyl cis or trans to vinyl) was subjected to ring expansion with a 15% defect of base, *cis*-5-methylthiacyclooct-4-ene was obtained as the major product with minor amounts of the trans isomer and β-elimination product (4-methylenehex-5-en-1-yl methyl sulfide) also present (10:0.6:1 ratio). Recovery of starting sulfonium salt showed only trans salt (93% recovery). When the recovered trans salt was resubjected to ring expansion conditions only the ring opened sulfide (β-elimination product) was obtained. This does not exclude the possibility that the cis salt may form a small percentage of elimination product. Therefore, cis-trans isomerization can occur via a reversible proton abstraction at C_2. Even though the starting sulfonium salt may be trans, ring expansion products arise exclusively from the cis salt. Thus, the cis-cisoid vinyl rotamer is accessible allowing selective formation of a *cis*-thiacyclooctene. This is a marked deviation from what is observed with acyclic [2,3] sigmatropic rearrangements and may reflect the strain arising from the incipient trans double bond in what will become an 8-membered ring. The energy difference in the final products has been estimated at 10 kcal/mol.[28,29]

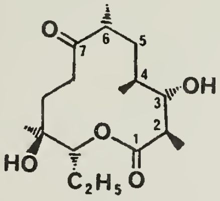
Similar results are obtained with ring expansion of a 1.5:1 cis:trans mixture of the hexafluorophosphate salt derived from 1,2-dimethyl-2-vinyltetrohydrothiopyran, in that 93% of the trans salt is recovered unreacted. The reaction produces *E*-5-methylthiacyclonon-4-ene exclusively. When the recovered trans salt was again subjected to ring expansion at -78°, no reaction occurred. On warming to -40°, however, a 7:3 mixture of E-olefin and β-elimination product are obtained.

Analysis of the geometry required for reaction to occur indicate that the E-olefin can be produced from the transoid rotamer of cis ylide, as this can be attained with minimal geometric adjustment.

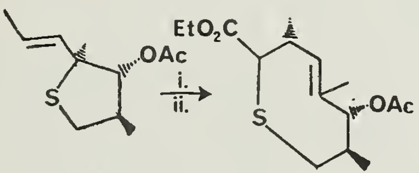
Thus, product stereochemistry is a function of product ring size. The 6-membered and larger rings resemble their acyclic analogues in that they rearrange to produce E-olefins. Only the 5-membered heterocycle reacts to produce product with Z-olefin geometry.

Methods are being developed for conversion of the ring expanded heterocycles into carbocycles.[24] Ramberg-Backlund sulfur extrusion has allowed conversion of activated sulfones into carbocycles in good yields (50-75%).[30]

Vedejs[31] has taken advantage of the predictable stereochemistry of the [2,3] shift in a new synthetic approach to macrolide antibiotics (such as 9), where a sulfur heterocycle incorporating the C_1-C_7 segment of the macrolide was constructed with natural stereochemistry at C_2, C_3 and C_6.



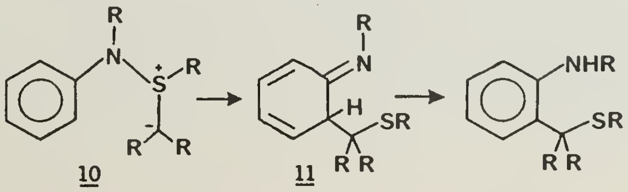
9



i. EtO_2CCH_2OTf
ii. DBU

Ortho Substitution. Alkylation of aromatic rings is typically done by Friedel-Crafts alkylation. The reaction is limited, however, by the difficulties associated with introducing n-alkyl groups or in carrying out the reaction on aromatic amines.[32] The use of a [2,3] sigmatropic rearrangement for the selective ortho substitution of an aromatic nucleus was first carried out by Sommelet and later was modified by Hauser.[20,33] Only recently has the reaction been expanded to N-aryl-N-azasulfonium salts, thereby allowing the ortho substitution of anilines.

The basic reaction is virtually the same as in ring expansion, except that the α-vinyl group has been incorporated into an aromatic ring. Ylides of the general formula 10 rearrange to give a dienone imine, 11, which on proton transfer and rearomatization gives an aniline which is alkylated exclusively at the ortho position.



Ylide formation is accomplished by treating an aniline, such as N-t-butylaniline, with a hypohalite, such as calcium hypochlorite, followed by reaction with dimethyl sulfide to produce an azasulfonium salt. Base treatment (sodium methoxide) affords the rearranged product. Raney nickel desulfurization then gives the ortho methylated aniline.

The reaction is not limited to N-t-butylanilines. Table 2[32,34] shows yields obtained from various para substituted anilines. Yields are uniformly good to excellent with a variety of substituents. Only para methoxy gave poor yields, due to the instability of the mono N-chloro derivative, which easily solvolyzes via heterolytic cleavage of the N-Cl bond.[32] This problem has been avoided by direct formation of the azasulfonium salt from the starting aniline by reaction with a halogen-sulfide complex ($RR'S^{+}X\ X^{-}$).[35] Yields of ortho-thiomethoxymethylanilines again are good, with slightly better yields obtained when electron donating groups are present, making this method complimentary to the first.

Table 2

p-X-$C_6H_4NH_2$	yield of ortho alkyl sulfide
H	90
Me	54
Cl	83
CO_2Et	65
NO_2	71
OMe	3

Various alkyl groups can be introduced with relatively minor changes in the sulfide. Tetrahydrothiophene allows introduction of an n-butyl group after Raney nickel desulfurization (63% overall yield from aniline). Similarly, tetrahydrothiopyran affords the n-pentylation product. Ortho benzylation can be achieved by using benzyl phenyl sulfide.

Sulfides which bear hydrogens β to the sulfonium cation undergo elimination if the aniline is unsubstituted, to give an azasulfide and alkene.[32,36] This limitation can be avoided in two ways. First, cyclic sulfides are less prone to undergo β-elimination because the β hydrogens are unable to attain the geometry necessary for elimination to occur. The second method[36] involves in situ acylation of a sulfilimine with acetic anhydride. This in turn will give an acyl protected azasulfonium salt which reacts with the generated acetate anion to produce an ylide which can undergo the typical [2,3] sigmatropic rearrangement.

Reaction regiospecificity is only of consequence in meta substituted anilines, where a slight preference for substitution para to the meta group is observed when the substituent is electron withdrawing.[32]

[2,3] Sigmatropic rearrangements provide two new routes for ortho formylation of anilines, and specifically, the easy preparation of ortho-aminobenzaldehydes, which are synthetically useful in carbostyril symtheses. Previous methods for ortho formylation included reduction

of ortho-nitrobenzaldehydes and oxidation of ortho-toluidines, both of which suffer from a lack of selectivity.[37]

The first new route takes advantage of the synthon aspects of 1,3 dithiane. For example, when aniline is treated with t-butyl hypochlorite followed by sequential treatment with 1,3 dithiane and sodium methoxide, ortho-aminobenzaldehyde trimethylene mercaptal is produced in 54% yield.[37] Para substituted anilines, for reasons that are not yet clear, give poorer yields (25-35%). Because dithioacetals are known to condense to oligomers, hydrolysis was preceded by amino protection with acetic anhydride. Hydrolysis is then accomplished with mercuric oxide-boron trifluoride etherate and sodium carbonate. This step gives excellent yields of acetaminobenzaldehydes (>90%).

An alternative method is to oxidize the sulfide after rearrangement of the azasulfonium salt.[37] When a mixture of aniline and thioanisole is treated with t-butyl hypochlorite followed by addition of sodium methoxide, o-thiophenoxymethyl aniline is produced in 61% yield. In this case yields are consistently good (60-70%), regardless of the nature of the aromatic substituent. Protection of the amino group, N-chlorosuccinimide (NCS) addition to produce an α-chlorosulfide, and finally hydrolysis, gives acetaminobenzaldehyde. In all cases, the chlorosulfide route was comparable to, or better than, the more elegant dithiane route. Table 3 summarizes the overall yields of both methods.

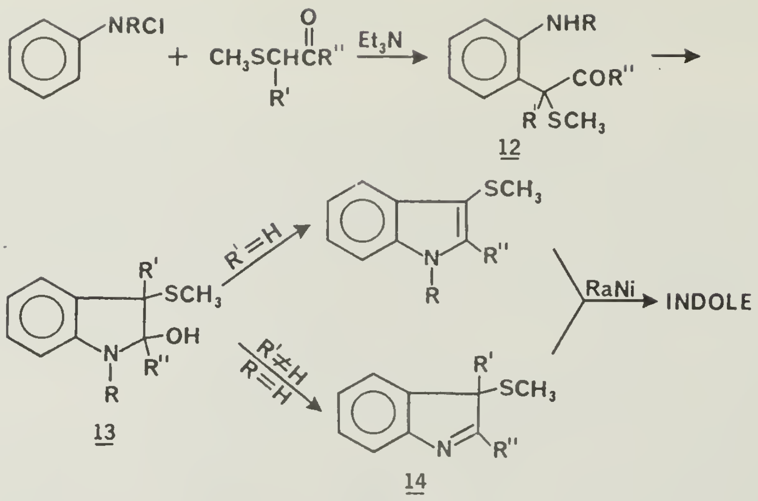
Table 3

Yield of o-acetaminobenzaldehyde

p-X-$C_6H_4NH_2$	via dithiane	via chlorosulfide
Me	21	33
H	44	45
Cl	24	50
CO_2Me	25	37

Ortho vinylation[37] requires an additional five steps after an o-thiomethoxymethylated aniline is obtained. Imide formation with acetic anhydride, α-chlorosulfide formation with NCS, oxidation to an α-chlorosulfone with m-chloroperbenzoic acid, acid catalyzed hydrolysis to a mono-N-acetyl derivative, and Ramberg-Backlund sulfur extrusion give 2-acetaminostyrenes in about 50% yield. Yields again remain fairly constant with a wide variety of substituents.

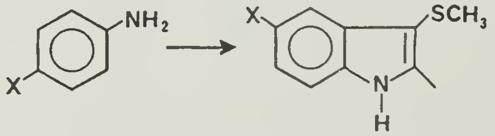
Perhaps the greatest success of Gassman's procedure is in the synthesis of indoles.[32,38,39] The classic method for indole synthesis has been Fischer's method, which involves rearrangement of a phenylhydrazone in the presence of a Lewis acid. The new method involves addition of a β-ketosulfide to an N-chloroaniline which forms an azasulfonium salt. Ylide formation is readily accomplished with triethylamine, since the methine proton is doubly activated. Rearrangement and rearomatization leads to an o-ketoaniline 12, which was isolable if the ketal was used. Intramolecular addition of the free amine with the carbonyl gives an α-aminoalcohol 13. Two modes exist for dehydration, depending on the nature of R (N substituent) and R' (sulfide substituent on carbon). When R = H or alkyl and R' = H, dehydration occurs across the 2,3 positions. Desulfuriza-



tion with Raney nickel, LAH, or sodium borohydride, depending on the nature of the substituents, produces the indole. When R = H and R' = alkyl, dehydration can procede across the $N-C_2$ bond to produce an indolenine, 14, which rearranges to a 3-substituted indole. Thus, a wide variety of unsubstituted, 2-substituted and 3-substituted indoles are available by simply varying the nature of the sulfide. This versatility has recently been exploited in the synthesis of anti-inflammatory agents and analgesics.[40]

As in the case of ortho alkylation, strong electron withdrawing groups on the aromatic nucleus, such as methoxy, render the N-chloroaniline unstable. This can be circumvented by replacing the sulfide with a halogen-sulfide complex.[35] The yields obtained from this process are complimentary to the original procedure, which had shown higher yields with electron withdrawing groups. The halogen-sulfide complex method shows highest yields with electron donating groups. This is likely due to the lower nucleophilicity of nitrogen when electron withdrawing groups are present, since nitrogen is then poorer at displacing halogen from the sulfide complex. Table 4[38,41] gives representative yields of the two procedures.

Table 4



	via sulfide	via halosulfide
OMe	0	38
H	69	68
Cl	72	45
CO_2Et	58	33

Ortho and para substituents on the aniline end up specifically at the 7 and 5 positions of the resulting indole nucleus, respectively. In the case of a meta substituent, either the 4 or 6 position may end up bearing the substituent. Reaction regiospecificity is apparently a function of the electronic character of the substituent.[38] Meta-toluidine gives a 3:2 mixture of 6 and 4 substituted indoles, while meta-nitroaniline gives the 4 isomer exclusively.

This procedure has several advantages over the classic Fischer synthesis. First, the procedure is a one pot reaction until desulfurization. Second, the reaction is isomer specific. Third, when R' and R" on the sulfide are joined as part of a cyclic structure, an easy route is available to tetrahydrocarbazoles. Fourth, the reaction is tolerant of a wide spectrum of substituents since there is little charge build up on the aromatic nucleus during the course of reaction. Fifth, starting materials are readily available. For 1-substituted indoles, Fischer's method requires a difficult to prepare 1,1-disubstituted hydrazine. Finally, the procedure employs mild conditions; no strong acids or bases are used and all steps are run at temperatures less than 0°.

Various other systems are easily accessible with minor modifications in the procedures just described. Oxindoles[42] can be prepared by replacement of the β-ketosulfide with a α-carboethoxy sulfide. Quinolones[43] can be obtained by using a substituted thiopropionate. Isatins[44] require only that a thiomethoxyindole (where R' = H) be treated with NCS, in order to replace the methine hydrogen with chlorine, followed by hydrolysis.

Methods have recently been developed which extend the methods developed for ortho substitutions of anilines to phenols.[45] Oxasulfonium salt formation is accomplished by reaction of an S-(N-succinimido)sulfonium halide or a halosulfonium halide at -25° with a phenol. Base treatment (triethyl amine) affords the oxasulfonium ylide which rearranges to produce an ortho substituted phenol. Formylation and alkylation products are obtained by the appropriate choice of starting sulfide.

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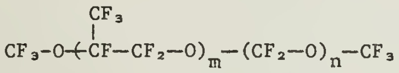
PHOSPHAZENES AS HIGH MOLECULAR WEIGHT MASS MARKERS

Reported by Chuck Snelling April 17, 1980

This report is on the mass spectra of high molecular weight compounds and the mass markers used to record them. The increasing use of mass spectrometry in the structure elucidation of natural products, particularly those of high molecular weight, has put great demands on currently available mass markers.[1,2] The most widely used mass markers for electron impact (EI) are polyfluoroalkanes (PFA) and perfluorotributylamine (PFTBA). PFA provides intense, regularly spaced peaks from m/e 50 to 850.[3] However, PFA can not be used in field desorption (FD) because it desensitizes the emitter. For positive ion chemical ionization (CI), Bowen[4] has had some success with perfluoro-s-triazenes, while McCloskey[5] reported the use of various perdeuterated hydrocarbon mixtures. Takeuschi[6] employed polymeric sulfur and phosphonitrile chlorides in negative ion CI. Ligon[7] has reported the use of a perfluorinated polyether, Fromblin-L 1, as a mass marker for FD from m/e 31 to 2000. Matsuo[8] reported the use of polystyrene, polyethylene glycol and polypropylene glycol as mass markers from m/e 300 to 11,000.



$$CF_3\text{-}O\text{-}(\overset{\displaystyle CF_3}{\overset{|}{C}}F\text{—}CF_2\text{—}O)_m\text{—}(CF_2\text{—}O)_n\text{—}CF_3$$

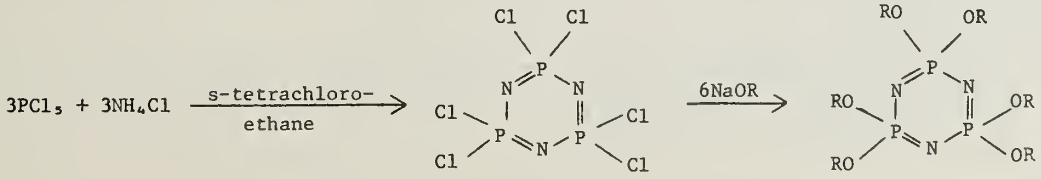
1

The great differences between the ionization processes in EI, CI, and FD mass spectrometry has led to a situation where no single reference standard exists for all three. However, if such a standard did exist, it would ideally exhibit the following characteristics:

1. Sufficiently intense peaks in the mass spectrum to cover a large mass range.
2. High volatility.
3. Minimal "memory effects" and minimal desensitization of the emitter in FD.
4. Negative mass defect for high resolution measurement.

Starting from the work of Olson,[9] we have continued the investigation of the chemistry of the multifluoroalkoxyphosphazenes and find them to be suitable reference standards for EI, CI, and FD mass spectrometry.

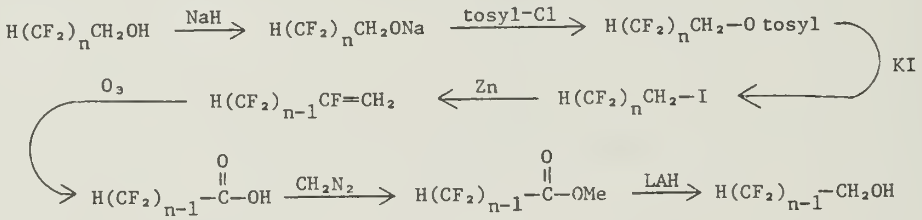
The starting material for synthesis of the phosphazenes is the 1,1,3,3,5,5-hexachlorocyclotriphosphazene ("trimer") 2 which is itself produced by the method of Rätz.[10] The "trimer" is reacted with the sodium salt of a polyfluorinated alcohol to produce a hexakis(multifluoroalkoxy)cyclotriphosphazene, 3.



2 3

For example, if the R group of 3 was 2,2,3,3-tetrafluoropropyl, the resulting phosphazene would have the systematic name 1,1,3,3,5,5-hexakis(2,2,3,3-tetrafluoropropoxy)cyclotriphosphazene. The EI spectrum of this phosphazene has a molecular ion at m/e 921 as the base peak with large peaks at m/e 902, 870 and 790. These latter peaks correspond to the loss of $F^\bullet$, $^\bullet CF_2H$, and $^\bullet OCH_2CF_2CF_2H$, respectively. The CI and FI spectra contain only the M+H and M+ ions at m/e 922 and m/e 921, respectively.

When alcohols of different molecular weight and concentration are used in the phosphazene synthesis, the mixture produced follows multinomial statistics. After investigating several mixtures, it was decided to use a series of binary mixtures rather than one complex mixture. This approach gives us flexibility to compensate for decreased volatility as the molecular weight increases. However, some of these mixtures require alcohols not commercially available. To prepare these alcohols, the following sequence of reactions was carried out:



With these alcohols, binary mixtures have been synthesized that cover the mass range from m/e 729 to 3321. Reference standards now can be prepared that cover as few as 200amu to as many as 2700amu. One data system available to us has been calibrated with these mixtures from 700-1700amu. Several samples that could normally be run only with an oscillographic recording device have been obtained with the computer. These mixtures have been used also for high resolution FD measurements.[11-12] Finally, it can be seen that phosphazenes not only fulfill all the criteria set forth earlier for reference standards but also are the only substances yet reported to be useful in all ionization modes.

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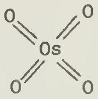
OXO OSMIUM(VIII) OXIDATIONS OF OLEFINS

Reported by Stephen Taylor April 21, 1980

The reaction of an olefin with osmium tetroxide (1) is the most reliable method for cis-dihydroxylation of a double bond,[1] especially when used in stoichiometric quantities with pyridine[2] (Table 1, entries 1-3). However, the great cost and toxicity of OsO_4 make this method prohibitive for large-scale reactions, hence the impetus for the development of procedures that use OsO_4 in catalytic amounts. Although other reagents, such as $KMnO_4$ and RuO_4, effect cis-dihydroxylation of olefins and are less expensive and toxic, OsO_4 generally produces higher yields of the desired diols and gives less of the overoxidized ketol and carbon-carbon cleaved products. In this report we review briefly the recent developments in the dihydroxylation of alkenes and alkynes with OsO_4 and then present the recent extension to oxyamination and diamination of olefins using reagents 2 - 4. Plausible mechanisms for these reactions will also be presented.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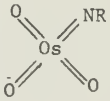
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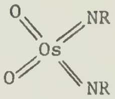
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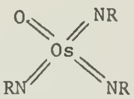
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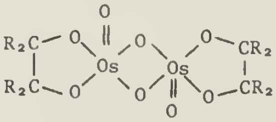
Stoichiometric OsO_4 Dihydroxylations. It has long been thought that OsO_4, like $KMnO_4$, reacts with mono-alkenes from the less hindered side to give intermediate cyclic cis-esters which upon hydrolysis (leaving the carbon-oxygen bonds intact) yield the corresponding cis-diols.[2,3] As the pH decreases, both reagents give an increasing ratio of ketol to diol product. OsO_4, RuO_4, and, in most cases, $KMnO_4$ exhibit gradual increases in the rate of addition to simple olefins with increasing alkyl substitution. The relative rate differences are increased in solvents of poorer coordinating ability (i.e., pyridine ⟶ ether ⟶ hexane).[4] OsO_4 and $KMnO_4$ differ significantly in their reaction with olefins containing electron withdrawing substituents. These substituents accelerate the permanganate oxidations while they retard the reactions of OsO_4.[5]

Reactions of OsO_4 with olefins in non-aqueous solvents produce the intermediate esters slowly in nearly quantitative yields. The addition of a tertiary amine (or especially pyridine) helps stabilize the osmate ester and significantly speeds its rate of formation.[2] The structures of the osmate esters were first postulated by Criegee[2] and recently confirmed by Griffith et al.[6,7] The studies of Griffith[6a] indicate that small olefins give either mono- (5) or di-esters (6) with OsO_4. Larger olefins such as cholesterol and ergosterol give only the dimeric mono-ester (5).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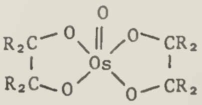
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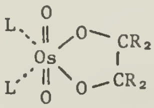
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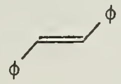
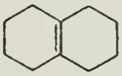
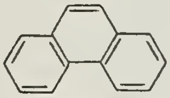
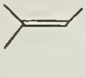
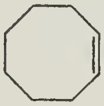
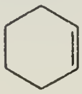
The X-ray crystal structure of the osmate ester formed from a stoichiometric amount of tetramethylethylene shows it to be dimeric (5) with square based pyramidal Os(VI) linked in a centrosymmetric structure via a dioxo-bridge. The terminal oxo-ligands (Os-O 1.673 Å) are trans to each other across the planar Os_2O_2 bridge (Os-O 1.92 Å).[7] On the other hand, the osmate ester formed with excess tetramethylethylene or from the mono-ester recrystallized from tetramethylethylene in CCl_4 gives an X-ray crystal structure consistent with the monomeric di-ester (6). Studies of IR spectra in the solid state or solution together with ^{1}H NMR suggest the same structures for the esters in solution as in the solid state. In the presence of tertiary amine bases, pyridine, or isoquinoline (L), complex 7, which contains a trans $O{=}Os^{VI}{=}O$ unit,[8] is postulated to be formed. Griffith[6b] also reported the isolation of several stable tertiary amine complexes of OsO_4 that are reactive toward olefins. These adducts show no appreciable vapor pressure at room temperature which might make their use favored over the very toxic and volatile OsO_4.

Various reagents have been used to effect cleavage of osmate esters, including: acidic solutions of sodium or potassium chlorate,[2a,9] sodium sulfite and zinc dust,[10] alkaline formaldehyde[11] or mannitol,[2a,12] sodium sulfite[13] or bisulfite[14] in aqueous alcohol, aqueous sodium bisulfite and pyridine,[15] lithium aluminum hydride,[16] hydrogen sulfide,[17] and sodium borohydride.[18] The most popular are sodium bisulfite, hydrogen sulfide, and alkaline mannitol.

Table 1. Cis-Dihydroxylation of Olefins

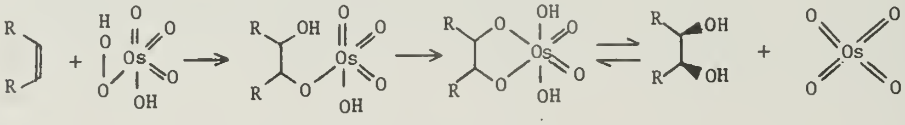
Entry	Olefin	Procedure	Isolated Yield	Reference
1		$KMnO_4$	14	5
		OsO_4	48	5
		OsO_4, pyridine	90	5
2		OsO_4	81	2a
3		OsO_4, pyridine	64	2b
4		H_2O_2[a]	40	20b
		t-BuOOH, Et_4NOH[a]	63	24a
5		$KMnO_4$	50	45b
		$NaClO_3$[a]	30	45c
		H_2O_2[a]	11	45c
		NMO [a,b]	79	26
6		$KMnO_4$[a]	33	45a
		$NaClO_3$[a]	46	45a
		H_2O_2[a]	58	20b
		K_2OsO_4, $NaClO_3$[a]	76	23
		t-BuOOH, Et_4NOH[a]	62	24a
		t-BuOOH, Et_4NOAc[a]	52	24b
		NMO [a,b]	91	26

[a] Catalytic procedure
[b] NMO = N-methylmorphline-N-oxide

Catalytic OsO_4 Dihydroxylations. Due to the great expense of using stoichiometric amounts of OsO_4 in large scale reactions, alternative procedures using catalytic amounts of OsO_4 have been developed. These procedures involve the use of a second oxidizing reagent which by itself is inert toward olefins. In each case the addition is cis but the mechanisms of these reactions have not been fully characterized.

The catalytic systems developed by Hoffman and Milas use metal chlorates[19] and hydrogen peroxide.[20] The reaction with metal chlorates is carried out in aqueous solutions and is postulated to proceed by addition of OsO_4 to the olefin, decomposition of the osmate ester, and regeneration of the tetroxide by the chlorate.[3,21] Procedures involving H_2O_2 use reaction mixtures ranging from anhydrous H_2O_2 in tert-butyl alcohol[20a,b] to 30% aqueous H_2O_2 in acetone-ether,[20d] with catalytic OsO_4 amounts as low as 0.2%. Milas[20c] proposed a mechanism involving addition of H_2O_2 to OsO_4 with subsequent addition to the olefin (Scheme I). A catalytic procedure using sodium hypochlorite as the oxidant has recently been reported in the literature.[22]

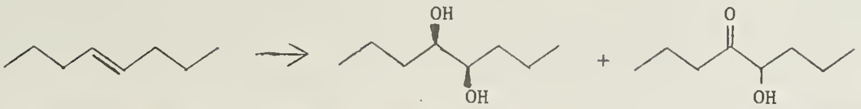
Scheme I



Lloyd et al.[23] reported a procedure that uses 0.2% potassium osmate with H_2O_2 or $NaClO_3$ (Table, entry 6). Nonvolatile potassium osmate is used to avoid the handling of pure OsO_4. It presents no handling or storage problems as long as it is kept dry. Reactions with olefins give yields comparable to those reactions using pure OsO_4.

Although the use of H_2O_2 or metal chlorates permits the catalytic use of OsO_4, with certain olefins these methods produce substantial amounts of overoxidized products. From the knowledge that basic conditions increase the yield of diol with $KMnO_4$, catalytic procedures using weak bases have recently been developed. A procedure developed by Sharpless et al.[24] employs Et_4NOH in tert-butyl alcohol with tert-butyl hydroperoxide and 0.2% OsO_4. Except in cases where the olefin is sensitive to base, the use of Et_4NOH generally affords better yields of diol than with the Hoffman (metal chlorates) or Milas (H_2O_2) procedures. With mono- and disubstituted olefins that are sensitive to overoxidation, this procedure is clearly superior as exemplified by the oxidation of (E)-4-octene (Table 2). In the case of less sensitive olefins, the yields are comparable, but with tri- and tetrasubstituted olefins, the Sharpless method is superior (Table 1, entry 4). Since the rate of reaction of OsO_4 is enhanced by increased alkyl substitution,[25] Sharpless[24] suggested that the low reactivity of tri- and tetrasubstituted olefins with the Hoffman and Milas procedures is a result of slow hydrolysis of the hindered osmate esters, which create a bottleneck in the catalytic sequence. The basic Et_4NOH could facilitate the hydrolysis and thus promote a faster turnover of the osmium catalyst.

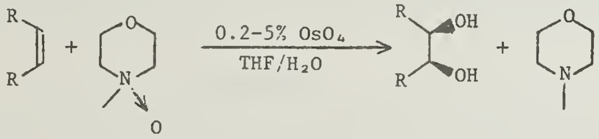
Table 1. Effect of Catalytic Procedure on Product Ratio



Conditions (0.2% OsO_4)	Ratio of Diol to Ketol	% Yield
t-BOOH, t-BuOH, H_2O, Et_4NOH, 0°	10	73
t-BuOOH, t-BuOH, H_2O, 0°	0.5	40
H_2O_2, t-BuOH, H_2O, 0°	0.6	<20
$KClO_3$, dioxane, H_2O, 50°	—	<5

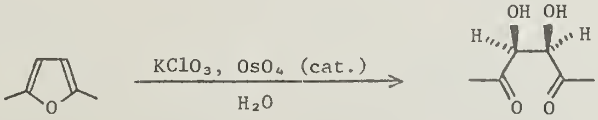
The substitution of Et_4NOAc in acetone for Et_4NOH permits the dihydroxylation of base sensitive olefins.[24b] Ethyl crotonate, for example, is not hydrolyzed and gives the diol in 72% yield with none of the epoxide which would arise if conjugate addition of tert-butyl hydroperoxide were a competing process. The yields from reactions with simple olefins are comparable to those using Et_4NOH but reactions with tetrasubstituted olefins fail. Both procedures fail with hindered olefins such as cholesterol, presumably due to the inertness of the hindered osmate ester to hydrolysis. This is consistent with the observation that olefins which fail to react in these systems are potent inhibitors of the catalytic process.

A recently developed catalytic procedure that is superior to most other procedures in terms of yield and diol to ketol ratios employs amine oxides, preferably N-methylmorpholine-N-oxide (NMO), as the oxidant (Eq. 1).[26] The yields with this method compare favorably with the tert-butyl hydroperoxide procedure but the reactions with tetrasubstituted olefins have failed so far (Table 1, entries 5,6).



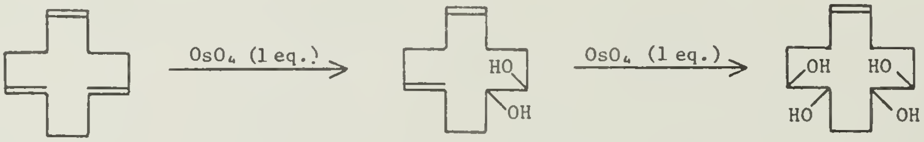
(1)

Reactions with Dienes and Alkynes. Criegee[2b] established that conjugated dienes form 1,2-, not 1,4-, adducts. However, 1,4-dihydroxylation has not yet been ruled out in the recently reported oxidation of 2,5-dimethyl furan (Eq. 2).[27]



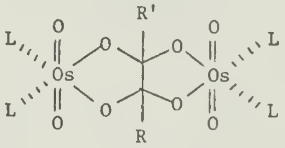
(2)

Diols may be prepared from dienes using one equivalent of OsO_4 with pyridene and hydrolyzing the precipitated mono-ester. The use of excess OsO_4 produces tetrols.[6c] The Milas catalytic procedure generally gives tetrols.[20b,28] Studies by Ohno and Torimitsu[29] have shown that OsO_4, like $KMnO_4$, exhibits a high selectivity toward *trans*-olefins (Eq. 3).



(3)

From the reaction of diphenylacetylene, phenylacetylene, and methylphenylacetylene with OsO_4 and pyridine or isoquinoline, Griffith[6c] isolated the intermediate osmate esters and characterized their structures as *8*.



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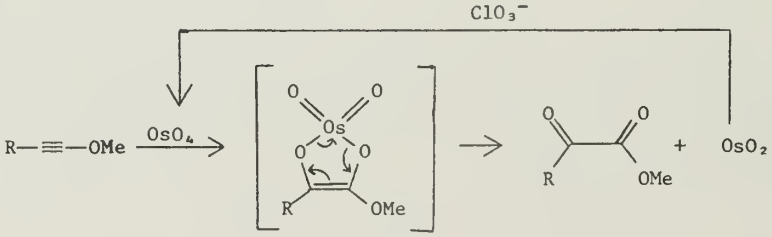
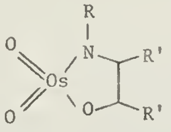
L = pyridine or isoquinoline

Hydrolysis of the diphenyl- and methylphenylacetylene gives predominantly the α-keto product while phenylacetylene gives only the overoxidized product, benzoic acid. Catalytic hydroxylation of diphenylacetylene using $KClO_3$ produces the α-diketo product in good yields but the use of H_2O_2 gives only overoxidized products.[30] Re *et al*.[27] reported that the use of $KClO_3$ in the catalytic oxidation of acetylenic ethers gives the corresponding diketo compounds in moderate to good yields. The proposed mechanism (Scheme II) does not include the intermediate osmate ester, *8*, because of the relatively low concentration of OsO_4.[27]

Scheme II



Oxyamination and Diamination. In a reaction analogous to dihydroxylation with OsO_4, Sharpless *et al*.[31] reported the stereospecific vicinal oxyamination of olefins by alkylimidoosmium compounds, *2*, where R = *tert*-butyl, *tert*-amyl, or 1-adamantyl. The addition of these reagents, which are easily synthesized in high yields, to olefins is exclusively cis and is, in most cases, highly regioselective with the formation of the new carbon-nitrogen bond at the less hindered carbon. Only $LiAlH_4$ (when no $LiAlH_4$-labile functional groups are present) and bisulfite have been found to cleave the osmate esters, 9, in good yield.



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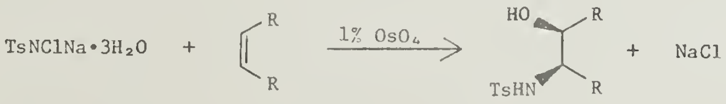
Solvent is an important factor in the oxyamination reaction. The amino alcohol to diol ratio increases with the coordinating ability of the solvent. Analogous to OsO_4 reactions, the addition of pyridine enhances the rate of reaction and reduces the yield of overoxidized products. Unlike OsO_4, though, increased alkyl substitution of the olefin decreases the rate of reaction. Increased steric hindrance of the olefin increases the ratio of diol. Tetramethylethylene affords only the diol in 82% yield. Conjugation of the olefin to an aromatic ring increases the rate of reaction and exhibits a slight preference for carbon-nitrogen bond formation adjacent to the aromatic ring. Inductive electron withdrawing groups have little effect on the reaction rate but geometry of the olefin has significant effect. (E)-isomers react 5 times faster than (Z)-isomers, which is analogous to Ohno's[29] observations with OsO_4. The (E)-isomers also give greater amino alcohol to diol ratios. A Hammett study of a series of para-substituted α-methylstyrenes gave U-shaped curves in both CH_2Cl_2 and pyridine.[31] Dondoni[32] observed a similar phenomenon for the 1,3-dipolar addition of nitrile oxides to para-substituted styrenes. Firestone[33] rationalized the U-shaped plot obtained by Dondoni by suggesting that the 1,3-dipolar addition proceeded with diradical character in the transition state, and, as such, X groups conjugated to an unsaturated radical center will stabilize the radical intermediate relative to $X = H$. It is interesting to note that Henbest found that the addition of OsO_4 to a series of para- and meta-substituted stilbenes gives a normal Hammett plot with $\rho = 0.55$.[5]

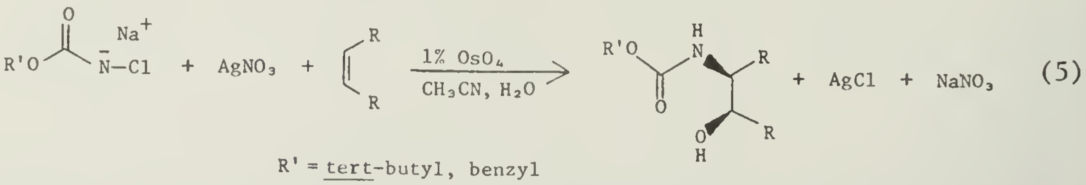
Oxyamination by alkylimidoosmium reagents has two major limitations: a stoichiometric amount of osmium reagent is required and the *tert*-alkyl groups are difficult to remove. Consequently, Sharpless *et al.*[34] developed a procedure that uses Chloramine-T in the presence of a catalytic amount of OsO_4 for the *in situ* regeneration of imido species 2 ($R = Ts$) to afford *cis*-hydroxy-*p*-toluenesulfonamides from olefins (Eq. 4). This procedure



(4)

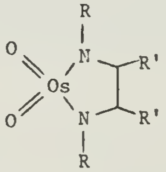
overcomes the first limitation but the sulfonamide protecting group is sometimes difficult to remove. In addition, this procedure fails with many hindered tri- and tetrasubstituted olefins. Bäckvall and Sharpless[34a, 35] have explored a number of high yield transformations of hydroxy sulfonamides.

Sharpless[36] also developed a catalytic OsO_4 procedure that utilizes the in situ production of N-chloro-N-argentocarbamates to produce cis-hydroxy carbamates (Eq. 5). The nitrogen now bears a leaving group that



is easily removed. This procedure is more effective with electron deficient olefins than the Chloramine-T based procedure but is less effective with trisubstituted olefins. However, Sharpless has observed that addition of Et_4NOAc may improve its effectiveness with hindered olefins. The regioselectivity of the N-chloro-N-argentocarbamate procedure is much better than that with Chloramine-T but neither catalytic procedure can compete with the regioselectivity exhibited by the stoichiometric tert-alkylimidoosmium reagents. Although a number of methods are available for the synthesis of β-amino alcohols, only these methods developed by Sharpless permit direct cis addition of oxygen and nitrogen moities to an olefin.

Sharpless[37] also prepared and isolated the di- and triimidoosmium complexes 3 and 4 (R = tert-butyl) in moderate to good yields. Like the monoimidoosmium complexes (2), these complexes show a great preference for the addition of nitrogen over oxygen. Hydrolysis of osmate complexes 10 and 11 gives the cis diaminated olefins. Only one other case of direct



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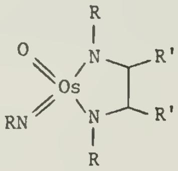

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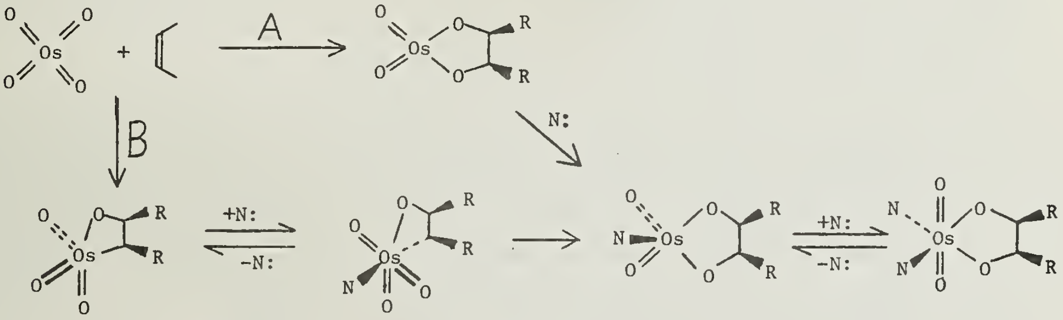
vicinal diamination has been reported.[38] In contrast to OsO_4 reactions, oxidations of olefins by 3 and 4 are accelerated by electron withdrawing groups. Both complexes are remarkably unreactive toward cis-disubstitued olefins. For example, 3 reacts with cyclohexene to give only the hydroxy amine whereas 4 has no reaction at all. Ratios of diamines to hydroxy amines are insensitive to solvent coordination ability, unlike reactions with the monoimido complexes. The triimido complex tends to be more reactive toward very electron deficient olefins whereas the diimido complex is more reactive toward dialkyl and aryl substituted olefins.

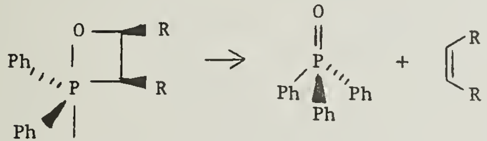
The X-ray crystal structure studies on mono- and diimidoosmium complexes,[39] comparisons with isostructural M = O and M = NR complexes, and spectral studies[37] all indicate significant osmium-nitrogen triple bond character in the imidoosmium complexes. This is expected because of the lower electronegativity and greater π-donor capability of nitrogen versus oxygen.[39]

Alternative Mechanism. The reaction of OsO_4 with olefins has long been accepted to proceed by a [3 + 2] cycloaddition process (path A, Scheme III).[2] Sharpless,[40] though, has proposed an alternate mechanism (path B) which involves a four-membered ring organoosmium intermediate.

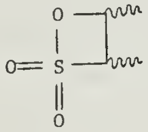
Scheme III



This mechanism is analogous to the mechanism which best explains the chromyl chloride oxidation of olefins.[40] Sharpless prefers nucleophilic attack on osmium in the [2 + 2] case over nucleophilic attack on oxygen in the [3 + 2] case. The first step (path B) can be seen to be essentially the microscopic reverse of the olefin-forming step in the Wittig reaction where a trigonal bipyramidal oxyphosphetane (12) decomposes to a tetrahedral phosphine oxide (13) and an olefin.[41] In addition, SO_3 has been



12 13



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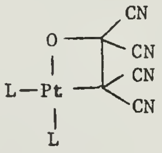

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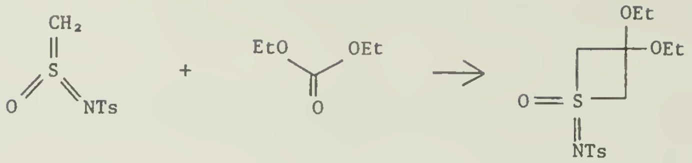
shown to undergo stereospecific [2 + 2] cis addition to (E)- and (Z)-2-butene to give the corresponding β-sultones (14).[42] A platinum complex with the same structural features (15) has also been characterized.[43] In the reactions of imidoosmium complexes, precedence for the selection of nitrogen over oxygen is exemplified by the reaction of an iminosulfene with an enol ether to give a [2 + 2] adduct (Eq. 6).[44] For all known [2 + 2] and [2 + 4] additions of other similar sulfur compounds with olefins and dienes, a rule of selection (C > N > O) appears to hold.[45]



(6)

Summary. Osmium tetroxide generally gives higher yields of *cis*-diols from the dihydroxylation of olefins than other common oxidation reagents such as $KMnO_4$. Its use, however, has been limited because of its high cost, volatility, and toxicity. Recently developed procedures, though, that use catalytic amounts of OsO_4, give yields that are comparable to those using stoichiometric amounts. The use of potassium osmate may eliminate the need to handle pure OsO_4. The use of nitrogen analogs of OsO_4 provides a synthetically useful means of direct *cis*-oxyamination and diamination of olefins.

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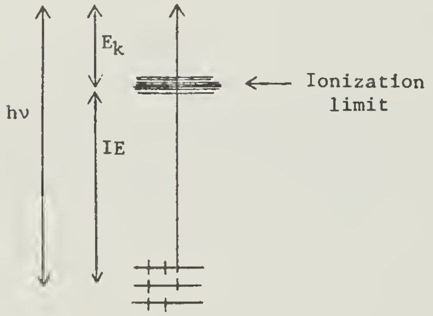
SOME RECENT USES OF UV-PHOTOELECTRON SPECTROSCOPY FOR THE STUDY OF N-HETEROCYCLES

Reported by Sander Mills April 24, 1980

The usual way of describing the chemistry of heterocyclic compounds is the qualitative valence bond formalism. However, it reaches its limits in attempting to describe the effects of repeated annelation and substitution. Molecular orbital theory can more effectively model these systems, but calibration and verification are difficult to come by. Experimental results dealing with observables MO theory predicts could accomplish this. Presently, the most direct method is photoelectron spectroscopy (PES), which, to a first approximation, displays the orbital energies of a system, thus providing an actual picture of the valence electronic structure of a molecule.[1]

The PES experiment is performed essentially as follows. A sample, in an evacuated chamber, is irradiated with high energy monochromatic light. The radiation can transfer energy to the electrons in the sample. If the transferred energy is great enough, it will excite an electron beyond the ionization threshold of the molecule.[1a,b] This process is illustrated in Figure 1.

Figure 1. Schematic of photoelectron ionization



$\boxed{h\nu = IE + E_k}$, where
hν = energy of light,
IE = ionization energy, and
E$_k$ = kinetic energy of free electron

All electrons with IE ≤ hν can be ionized, though only one per molecule. For the examination of the valence electrons of organic compounds[2] in the gas phase (to which this review will be limited[3]) UV light is generally used, since it provides better resolution than higher energy (i.e. X-ray) sources.[1b,c] The sources almost universally used for UV-PES are the helium I and helium II emission lines, at 21.2 and 40.8 eV, respectively.[1b] With these sources, a resolution of 0.01 eV is possible.[1b]

Clearly (from the equation in Figure 1), if the emitted electron's kinetic energy is known, the IE's for each electron can be determined. A plot of the number of electrons detected against their kinetic energy, then, should display maxima at energies corresponding to the ionization energies of the molecular orbitals. However, this requires that each ionization event correspond to a molecular orbital, an approximation, since it demands that no orbital realignment occur on going from a closed shell system to an ion. Koopmans Theorem[1c,4] is the quantum mechanical justification for this approximation. It states that, in the absence of electron correlation, relativistic effects, or orbital realignment, each molecular orbital will yield one ionization band, and the bands will remain in the same energetic order as the molecular orbitals from which they originated. Although this assumption is sometimes suspect,[5] it usually provides correct orderings of MO's, even if the energies are shifted somewhat. It is almost universally assumed for routine spectral interpretations. As a result, MO calculations[1c,5,6] occupy a central role in the elucidation of photoelectron spectra, since they can provide both approximate energies for orbitals and give electron density maps of each MO. Perturbation molecular orbital theory is also a powerful method for the qualitative interpretation of spectra.[7]

The most important factor affecting the photoelectron spectrum's appearance is vibrational fine structure. Fine structure results from the different population of various vibrational levels of the ionic system. These vibrational peaks (the Franck-Condon envelope) can provide information about the bonding in the ground state MO.

The broadening due to vibrational structure makes reporting a single ionization energy for a band potentially ambiguous. Instead, either the adiabatic IE or the vertical IE are cited. The adiabatic IE corresponds to a transition between the ground state and the ground vibrational level of the ionic state, and is the lowest energy peak in a band. The vertical IE is the energy difference between the most probable vibrational state in the ion and the ground state. It is the most intense peak in a band, and is the band usually reported.[1b]

Other factors affecting spectral appearance, such as spin-orbit coupling, Jahn-Teller effects, and source dependent intensity changes,[8] have been reviewed;[1c,d] their use is in conjunction with ionization energies and calculations, facilitating the assignment of orbitals.

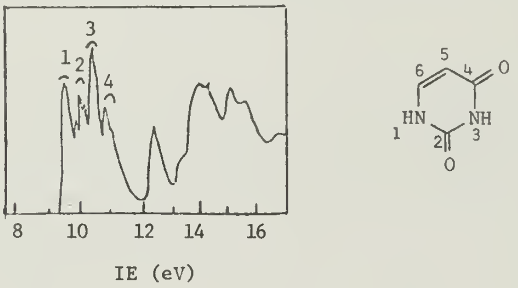
In organic chemistry, PES displays significant limitations, but within these, a variety of uses. The major limitation is the complexity of the spectrum; except for small systems or those with high symmetry, band overlap generally obscures the greater part of the spectrum. Assigning bands that lie within the sigma manifold (IE ≥ 13-14 eV) is usually futile. The lower energy bands (usually of π or lone pair origin) are better isolated and can be studied. However, it is these latter bands, the highest occupied molecular orbitals (HOMO's) that contain most of the information about reactivity and kinetic stability anyway. The general necessity of using Koopmans approximation has been discussed above. For organic molecules, sophisticated calculations have shown that the approximation fails completely only for the higher IE bands (>15 eV).[5]

Organic PES emphasizes the use of small structural changes in examining a system. Because of the relatively large size of organic molecules, these changes can be treated as local perturbations on the system. Thus, comparison of closely related systems: 1) the sensitivity of the system to substituents at different sites, and 2) the general effect of a substituent, in a quantifiable way.[2,10,11] UV-PES has also been used for the identification of conformers[12] and tautomers (vide infra) in the gas phase, for the analysis of through space and through bond effects,[13] and for the correlation of UV-PES with regular UV spectroscopy.[14,15]

Applications in Heterocyclic Chemistry. The biological importance of the pyrimidine and purine systems has stimulated a number of UV-PES studies.[16-20] Particularly well-studied is uracil.[18-20] An examination of the techniques used to analyze this system provides an overview of useful (and questionable) methodologies.

LeBreton and his associates[18,19] used a substituent approach in their study of uracil, in which an initial PMO theory model was tested and refined by comparison of the experimental and theoretical results of substituents. Their analysis began with the photoelectron spectrum of uracil (see Figure 2). Several low energy bands are present, and two (2 and 4) possess noticeable, but complex, vibrational structure. In band 4, a spacing of 1600 cm^{-1} was noted, and this was correlated with a carbonyl stretch. On the basis of this observation, model compounds, and INDO calculations, bands 2 and 4 were assigned to the MO's resulting, respectively, from the antibonding and bonding combinations of the oxygen lone pairs (see Figure 3).

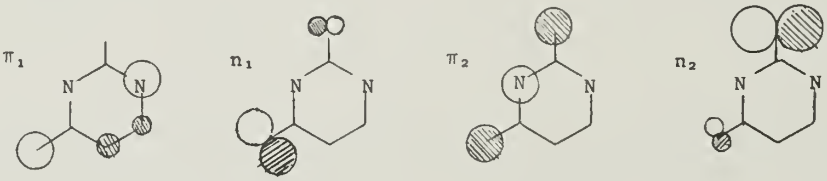
Figure 2. Photoelectron spectrum and ionization energies of uracil



Ionization Energies (eV)

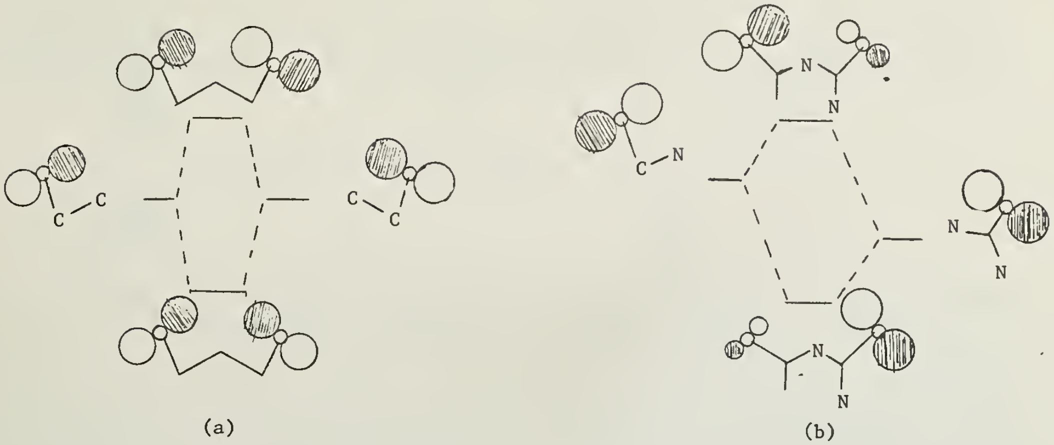
1) 9.5
2) 9.8-10.3
3) 10.56
4) 10.9-11.4

Figure 3. Highest occupied molecular orbitals of uracil



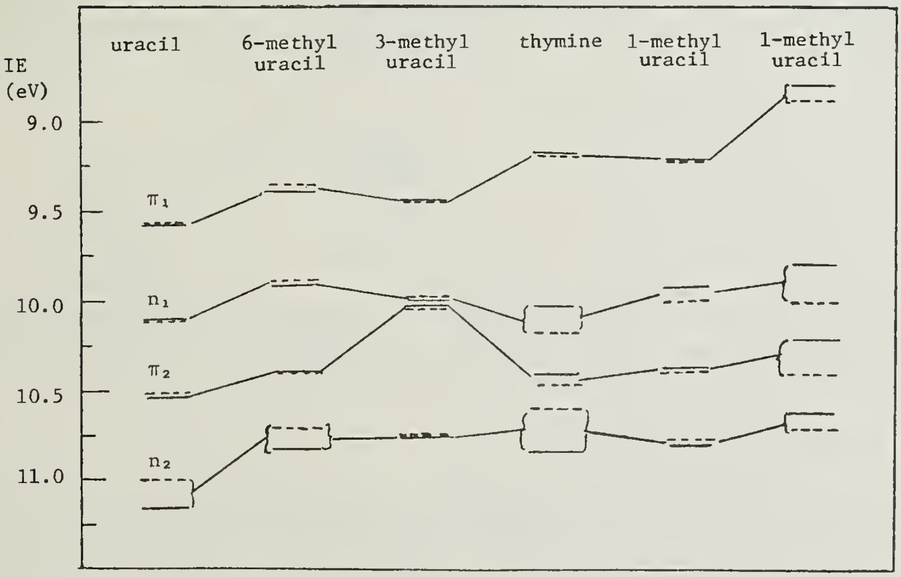
These bands are split by one eV, and LeBreton et al. attempted to show that such a splitting is reasonable by noting that it lies between that seen in a para dicarbonyl compound (benzoquinone, .3 eV) and an ortho dicarbonyl system (glyoxyl, 1.6 eV).[18a] Though the figures are consistent, the analogy is misleading. In the model compounds, two identical carbonyl fragments are interacting. The new MO's will contain identical coefficients on identical atoms (see Figure 4a). In uracil, the two carbonyl fragments are not equivalent, nor are they degenerate in energy. Though they end up one eV apart, a significant portion of the splitting was present prior to their interaction, adn the new MO's resulting from their interaction are shifted only slightly from their forms prior to interaction. Figure 4b represents the INDO electron density map of these MO's.[18a] A better approach would be to use models for each fragment, and assign the splitting from there.

Figure 4. Comparison of the interaction of like and unlike carbonyl fragments



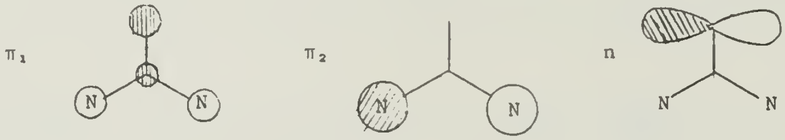
The first and third bands in uracil were assigned to π-type orbitals.[18a] LeBreton et al. used methyl substitution to test these assignments. Methyl groups, as electron donating units, should destabilize most of those orbitals that have the largest coefficient on the atom to which the methyl is attached. The five methyl substituted isomers used are listed in Figure 5, where a comparison of the INDO calculations and the experimental results are given.[18c] The excellent agreement strongly supports the assignments given above. Further support for this is that the lowest energy transition in the UV spectrum of uracil is of π* ⟵ π type, indicating that the HOMO is a π orbital.[18,22] (Assignments based solely on such criteria have been criticized, however,[23] because of differential electronic repusion terms in the description of an ionic state versus an excited state.)

Figure 5. Experimental (——) and INDO calculated (---) vertical ionization energies for methylated uracils. INDO values are normalized to HOMO of uracil.



McGlynn et al.[20] approached the study of uracil in a different way. They utilized a series of progressively more complex molecules, starting with urea, to "build up" the spectrum of uracil.[21] An understanding of the electronic structure of urea was essential to this, and hence a series of methylated ureas was examined. These displayed a regular destabilization of the π-type orbitals on methylation, and a much smaller effect on the lone pair orbital, resulting in an increasing separation of the n orbital from the π orbitals (see Figure 6). The uracil framework itself

Figure 6. MO's of urea

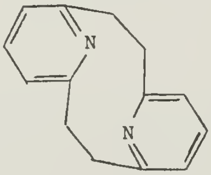


was approached via formylurea, acetylurea, and dihydrouracil. Formylurea was assigned by analogy to urea; this assignment was consistent with subsequent CNDO calculations and determination of substituent effects.

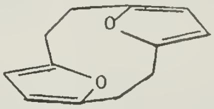
Though the different approaches agree here, this is by no means a certainty. As with any structure determination, the most convincing assignments are those that are consistent with the widest range of data. By that criteria, the assignment of uracil is well established.

Through space and through bond interactions, though purely mental constructs, have proven very useful in understanding the ordering of MO's in a variety of systems.[1g,13,24] "Through space" describes interactions resulting from the direct overlap of orbitals; "through bond" refers to the coupling between two orbitals by virtue of their mutual symmetry-allowed interaction with a third semi-localized orbital.[1c] Their separation can be accomplished through the judicious application of perturbation molecular orbital theory to photoelectron spectra.[24] This has been done for [2,2]-metacyclo-2,6-pyridophane (1),[25] and the results used as a model for [2,2]-2,5-furanophane (2) and [2,2]-2,5-thiophenophane (3)[26] (see Figure 7).

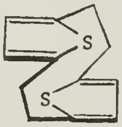
Figure 7



1



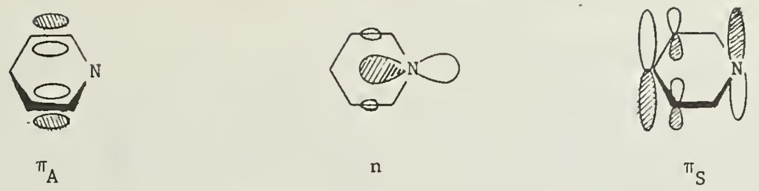
2



3

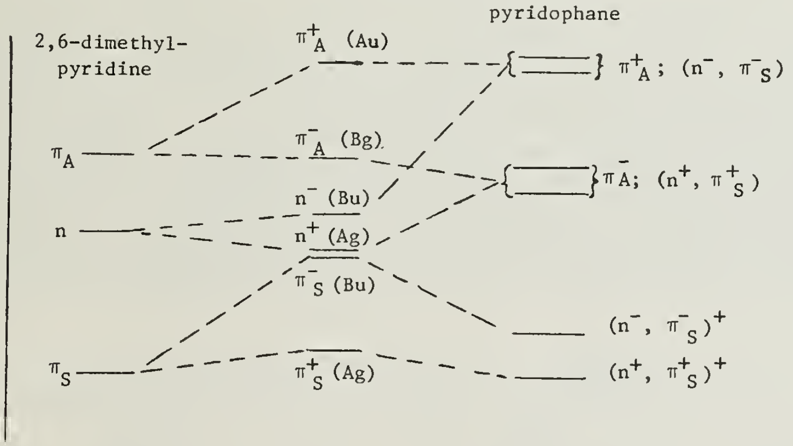
An X-ray crystal structure of 1 showed that it is centrosymmetric and has nearly C_{2h} symmetry.[27] The hydrocarbon portion of the rings are planar and nearly parallel to each other, with the nitrogens not quite over each other. The pyridophane MO's were built up by considering the interactions of two 2,6-dimethylpyridine fragments. The relevant MO's are π_A (8.9 eV), n (9.3 eV), and π_S (10.05 eV) (see Figure 8). These fragments are

Figure 8. HOMO's of pyridine



combined initially by combining like orbitals to form the pyridophane framework. The bonding and antibonding combination of π^+_S and π^-_S is strongly split, due to their extensive overlap, while the other two pairs interact less effectively. These new orbitals are now combined with the bonding and antibonding combinations of the ethylene bridge σ bonds. By symmetry, the σ^-_{CC} MO strongly interacts with the π^+_A orbital, destabilizing it considerably. π^+_S interacts with σ^+_{CC}, being raised in energy in the process. Finally, all orbitals of the same symmetry interact; n$^-$ and π^-_S mix, as do n$^+$ and π^+_S , to create the highest occupied molecular orbitals for 1. This process is illustrated in Figure 9.

Figure 9. Qualitative PMO diagram for pyridophane. Symmetry designations for C_{2h} point group are in parentheses.



The photoelectron spectrum of 1 has bands at 8.35, 8.46, 8.93, 9.08, 9.80, and 10.03 eV, in qualitative agreement with the PMO analysis. Through bond interactions between π^+_A and σ^-_{CC} and π^+_A and σ^+_{CC} serve to destabilize the bonding π combinations; for π^+_A this assigment requires inversion of the usual $IE_{bonding} \geq IE_{antibonding}$ ordering, as has been seen in other through bond interactions.[13]

For 2 and 3, whose X-ray structures place the heteroatoms above each other (in 2) and over the center of the other ring (in 3), PES indicates four low energy ionization events, with extensive overlap obscuring the precise ionization energies. Assignments for these bands are made by analogy to 1, and were qualitatively aided by CNDO/2 calculations. In both cases, the π^{+}_{3} MO (see Figure 10) is given as the HOMO (above π^{-}_{3}), and π^{+}_{2} is assigned above π^{-}_{2}, in both cases reversing the conventional ordering.[7] Interaction of the π system of one ring with the n orbital of the other decreases in the order 1 > 3 > 2, which would be predicted on the basis of resulting overlap[25] (see Figure 11).

Figure 10. HOMO's of five-membered aromatic heterocycles

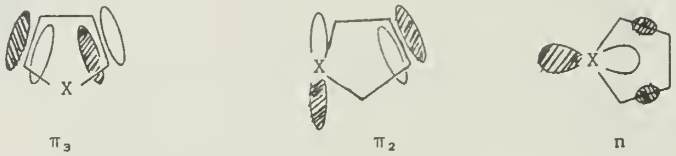
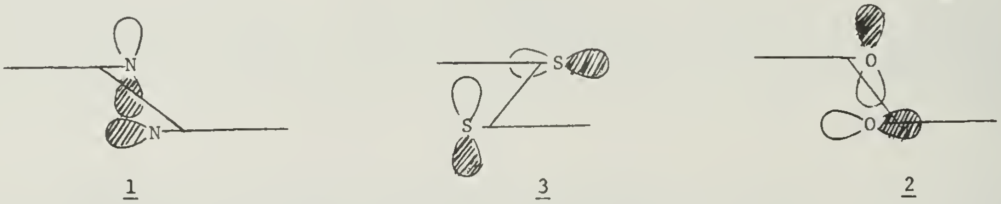
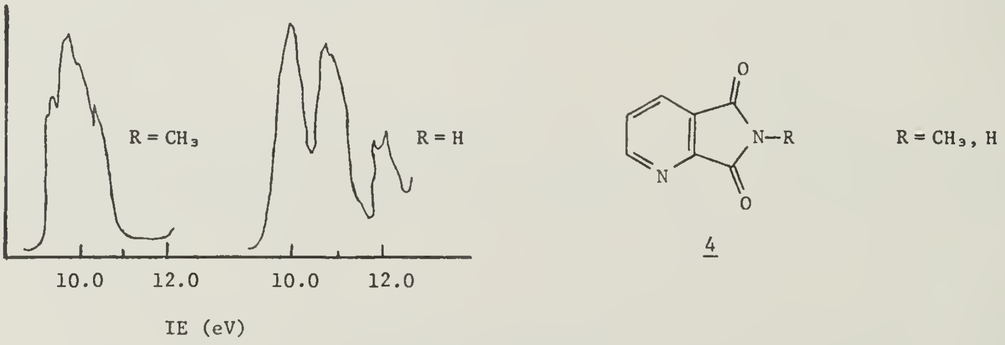


Figure 11



The determination of the relative abundance of heterocyclic tautomers is of continuing interest,[30] and UV-PES has been shown to be of use in elucidating gas phase tautomer structure.[31-33] Distefano et al.[33] combined UV and X-ray PES with IR and NMR measurements to assign the gas phase structure of quinolinimide (4), which displays a UV-PES spectrum significantly different from that seen in its N-methyl isomer (see Figure 12), and which showed no temperature or time dependence. The X-ray spectra also display differences between the two compounds not ascribable to methyl substitution. The IR spectrum of 4 does not possess an NH stretch near 3200 cm^{-1}, but shows a complex pattern below 3000 cm^{-1}. NMR studies indicate that the proton α to the pyridine nitrogen exists in two discrete environments in solution, implying that the pyridine nitrogen is involved in hydrogen bonding. A dimeric structure is postulated for solution, and

Figure 12. Structure and PES of quinolinimides



an intramolecularly hydrogen-bonded system for the gas phase.[33] Spectral simulation via Extended Huckel Theory calculations agrees better with the hydroxyimide from than with the regular imide tautomer.[33]

The difficulties involved in making definitive band assignments in PES have encouraged the development of other criteria for orbital assignments. A promising experimental technique which is coming into increasing use is the determination of the angular distribution of band intensities. The angular distribution of photoelectrons[1c,d] can be measured by rotating the elctron detector with respect to the source. The angle θ from source to sample to detector is a parameter upon which the relative intensity of photoelectron bands depends.[1c] This dependence is expressed in Equation 1, where σ_{av} can be related to relative intensity, $\sigma/4\pi$ is a constant for a given band, θ is as defined above, and β is a constant for a specific vibronic level of the ionic state; it is designated the assymmetry parameter, and ranges in value from -1 to 2. It can be determined simply by measuring intensity at two different angles.

$$\sigma_{av} = \left(\frac{\sigma}{4\pi}\right)\left[1 - \frac{1}{4}\beta(3\cos^2\theta - 1)\right] \tag{1}$$

The important parameter here is β, which is characteristic of the type of orbital from which the electron was ejected. Calculation of β theoretically is presently impossible except for very small systems.[1d] However, for some molecules, empirical correlations between β and orbital character have been established. Kobayashi has proposed some simple guidelines for β correlation.[34a,b] He suggests that for a pair of orbitals $\Phi^+ \Phi^-$ (i.e., n^+n^-), the more localized they are on their parent atom or group, the more similar β will be. A rough correlation has been shown among values of previously assigned orbitals of benzene derivatives.[34b] For pyridine,[36] 1,3,5-triazine and pyrimidine,[34c] Table 1 lists β and orbital assignments. For orbitals of π symmetry, β ranges from 0.65 to 1.33. Though the range is broad, in every case these are higher than the values for n and σ orbitals.

Table 1. Comparison of β and Orbital Type for Some Azabenzenes

System	IE	Orbital Type	β
pyridine	9.66	n	0.5
	9.80	π	0.65
	10.54	π	0.85
	12.48	σ	-0.3
1,3,5-triazine	10.4	n	0.43
	11.6	π	1.16
	13.2	n	0.39
pyrimidine	9.7	n_-	0.11
	10.4	π	1.33
	11.2	n_+	0.31
	11.4	π	0.68

Sell and Kupperman[35] used angular distributions of intensities to aid in the assignment of pyrrole, furan and thiophene. In addition to examining average β values for bands, they used the slope of β across the vibrational envelopes of the bands in an attempt to gain additional insight into the use of β for orbital assignments. Several π bands in pyrrole and furna have β slopes ranging from -0.45 to -1.5 eV^{-1}, which also are the largest values of β, while thiophene π band β's show no uniform slope. In pyrrole, a third π band cannot be located by either criteria; it is expected to be overlapped strongly by a series of σ bands.[35]

Clearly, these data are in need of extension and refinement. Their value, however, can be illustrated by the assignment of the third π band in thiophene, which had been in dispute for a decade.[35] The β measurement unambiguously shows this is the fourth band in the spectrum, at 12.4 eV.

The enormity of heterocyclic chemistry makes it difficult for the practicing chemist involved in heterocyclic work to gain an understanding of generally valid trends in chemical behavior, both of substituents and ring systems. The examination of the valence electronic structure of such systems, using UV-PES in conjunction with calculated models, the conceptual tools of PMO theory, and chemical behavior, can add another dimension to their views of organic chemistry.

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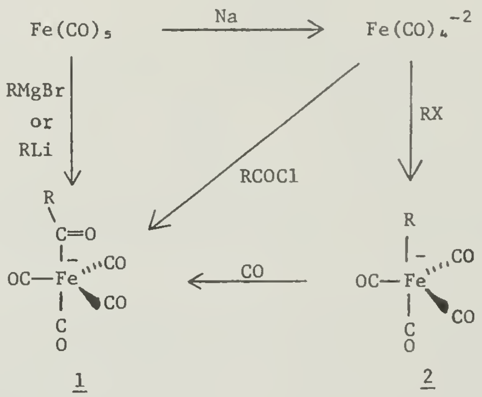
ORGANOTETRACARBONYLFERRATES(0) AS INTERMEDIATES IN ORGANIC SYNTHESIS

Reported by Munther Al-Aseer April 28, 1980

Organic chemists are increasingly interested in organotransition-metal chemistry as a source of novel synthetic methodology. In spite of extensive research, few truly useful organotransition-metal reagents have been developed due to complications such as side reactions, high costs of reagents and tedious work-ups. This review is a summary of the properties and applications of alkyl- and acyltetracarbonylferrates, stoichoimetric transition-metal reagents which function as acyl carbanion equivalents in the synthesis of common organic compounds.[1]

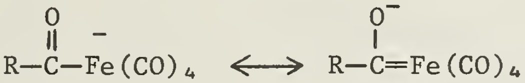
Preparation and Characterization. Acyltetracarbonylferrates (1) and alkyltetracarbonylferrates (2) are generated by several routes (Scheme I).

Scheme I



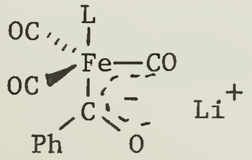
These air-sensitive complexes[2] are generally utilized, in situ, within a few hours of formation. Examples of ferrates 1 and 2 have been isolated and characterized spectroscopically in the solid (as salts)[3] and liquid[2] states. In solution, the infrared spectra of the acyl iron complexes are consistent with C_{3v} symmetry expected for trigonal bipyramidal coordination about iron(0) with the bulkier acyl group occupying an apical position. The terminal carbonyl groups exhibit stretching bands at 1870 - 2010 cm^{-1} while the acyl carbonyl group stretch occurs at 1550 - 1620 cm^{-1}, reflecting the high electron density on the acyl oxygen through back-bonding with the metal. The alkylferrates exhibit terminal CO bands which are slightly shifted to lower frequency relative to those of acylferrates. Such a shift is attributed to the higher electron density on iron in 2 and is in accord with the greater nucleophilicity of the alkyl anions.[4] An X-ray diffraction study[5] of $[(Ph_3P)_2N](CH_3CH_2CH_2Fe(CO)_4)$ shows a trigonal bipyramidal structure (C_{3v} symmetry) with the alkyl group in the apical position. Proton and ^{13}C NMR spectra, especially the observation of a single ^{13}C NMR signal, indicate rapid scrambling of the axial and equatorial groups.[6] Such scrambling is characteristic of many pentacoordinate complexes.[7]

The solution structure and geometry of ferrates 1 and 2 as ion pairs, complexed with cations such as Li, Na, MgX, etc., plays a significant role in some of the reactions of these complexes. Darensbourg[8] has undertaken a solvent effect study to determine the cation binding site in the alkyl- and acyltetracarbonylferrates. In the former, the cation is associated with the oxygens of the carbonyl groups. Of more interest is the cation binding site in the acyl anions. Due to the acyl ↔ oxy carbene resonance structure, the acyl group would seem to be the best binding site.



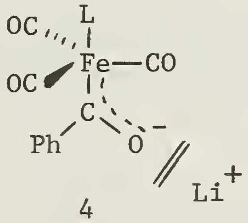
$$\mathrm{R{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}\overset{-}{Fe}(CO)_4} \longleftrightarrow \mathrm{R{-}\overset{\overset{\displaystyle O^-}{|}}{C}{=}Fe(CO)_4}$$

That this is in fact the case is indicated by the shift to lower frequency of the acyl carbonyl stretching band with smaller, less polarizable cations such as Li^+.[9] Furthermore, structural formulations have been proposed for the ion pairs in solvents which promote ion pairing (3) and in those which favor formation of free or separated ions (4).



3

$L = CO, nBu_3P, PPh_3$



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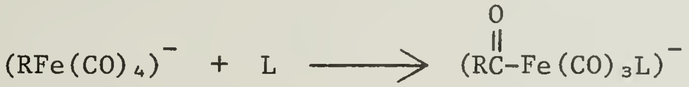
Though such formulations are highly speculative, they are borne out by differences in the reactivity of acylferrates in various solvents. For example, the iron acylates in THF are readily converted to the carbene derivative by treatment with the powerful alkylating agent $Et_3O^+BF_4^-$ *in situ*. In contrast, this reaction is not facile in diethyl ether. With common alkylating agents such as methyl iodide alkylation occurs either at the metal or at the acyl carbon. These reactivity patterns are suggested to arise from the ion-pairing effects. That is, only very strong alkylating agents, such as oxonium salts, are capable fo displacing the associated lithium cation and effecting alkylation at the acyl oxygen; weaker or softer alkylating agents, such as methyl iodide and methylfluorosulfate, "seek the next most negative site for reaction: the acyl carbon, iron or most reasonably the iron-acyl carbon-acyl oxygen electron sink, centering at acyl carbon".[10]

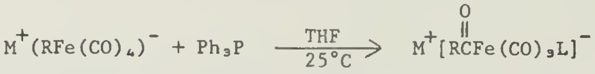
The Alkyl-Acyl Migratory Insertion Reaction. Ion pairing effects play an essential role in the mechanism of the alkyl migration reaction which transforms alkyltetracarbonylferrates into acyltetracarbonylferrates.[9,11]



$$(\mathrm{RFe(CO)_4})^- + \mathrm{L} \longrightarrow (\mathrm{R\overset{\overset{\displaystyle O}{\|}}{C}{-}Fe(CO)_3L})^- \qquad \mathrm{L = CO,\ PPh_3}$$

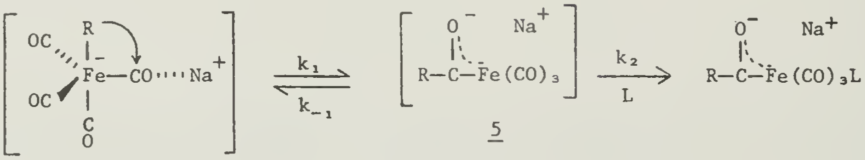
Conductivity studies reveal that $Na^+(RFe(CO)_4)^-$ in THF exists as a combination of ion pairs, dissociated ions and triple ions, the relative proportion of each being a function of the concentration of the alkylferrate. On the other hand, $Na^+(RCOFe(CO)_3L)^-$ exists predominantly in the ion pair form in the same concentration range ($10^{-2} - 10^{-3}$ M). The alkyl migration reaction is second-order overall, first-order in each reactant. The second-order rate constant varies significantly within a series of counterions (Table 1). The dramatic rate enhancement observed with alkali metal ions is thought to indicate that tight ion-pair transition states are more favorable than the more dissociated ones. Additional observations, such as rate inhibition by a change in solvent from THF to NMP (n-methylpyrrolidine) or HMPA, led to the proposal of the following pathway for the insertion reaction:

Table 1



$$M^+(RFe(CO)_4)^- + Ph_3P \xrightarrow[25°C]{THF} M^+[R\overset{O}{\overset{\|}{C}}Fe(CO)_3L]^-$$

M^+	k_{rel}
Li^+	1.0×10
Na^+	1.7×10
$(Na\text{-}Crown)^+$	1.0
$(Ph_3P)_2N^+$	0.42



ion pair

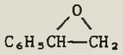
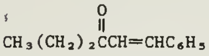
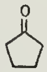
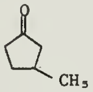
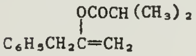
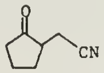
5

The initial equilibrium accomodates the observed ion pairing effects - i.e. migration is facilitated by Lewis acids, such as lithium cation, as they stabilize the unsaturated intermediate 5. More polar solvents inhibit the reaction by converting the contact ion pairs, the kinetically dominant species, to solvent separated ion pairs.

The alkyl-acyl migratory insertion reaction proceeds with retention of configuration at carbon as do other such reactions.[12] This is in contrast with the reaction of organic halides with $Na_2Fe(CO)_4$ to yield alkylferrates (Scheme I) - an oxidative addition or S_N2 displacement which results in inversion of configuration at carbon.[13]

Synthetic and Mechanistic Aspects. Over the last ten years the acyl- and alkylferrates have been shown to be intermediates in several novel preparative methods of organic compounds using iron pentacarbonyl. As acyl carbanion equivalents they have been utilized in the conversion of various organic halides into aldehydes, ketones, carboxylic acids, esters, etc. Scheme II shows the synthetic reactions while Table 2 lists typical product yields.

Table 2. Products and Product Yields for the Reactions of Alkyl- and Acyltetracarbonylferrates

No.	R	R'	Step in Scheme II	Product	Yield[a]	Ref.
	Ketones					
1.	S-(+)-*sec*-2 $C_6H_{17}OTs$	CH_3I	i,j	R-(-)-*sec*-$C_8H_{17}COCH_5$	(79)99ee.	4
2.	$Br(CH_2)_4CO_2C_2H_5$	C_2H_5I	i,j	$C_2H_5O_2C(CH_2)_4COCH_5$	(74)	4
3.	$CN(CH_2)_5CH_2Br$	*n*-$C_7F_{15}COCl$	i,j	*n*-$C_7F_{15}CO(CH_2)_6CN$	76	14
4.	$CH_3CH_2CH_2MgBr$	C_2H_5I	i,j	$CH_5(CH_2)_2COC_2H_5$	(78)	15
5.	CH_3Li	(*p*-$ClC_6H_4)_2I^+Cl^-$	i,j	*p*-$ClC_6H_4COCH_5$	(90)	16
	Acids					
6.	*n*-$C_5H_{11}Br$		h,k	*n*-$C_5H_{11}CO_2H$	97	17
7.	$ClCH_2(CH_2)_4CH_2Br$		h,k	$ClCH_2(CH_2)_4CH_2CO_2H$	(84)	17
	Esters					
8.	$CH_3(CH_2)_5CH(CH_3)OTs$	C_2H_5OH	g,l	$CH_3(CH_2)_5CH(CH_3)CO_2C_2H_5$		17
9.	*p*-ClC_6H_5CHO	*p*-ClC_6H_4CHO	g,l	$C_6H_5CO_2CH_2C_6H_4Cl$	(90)	33
10.	C_6H_5MgBr	C_2H_5OH	g	$C_6H_5CO_2C_2H_5$	(82)	27
11.	*n*-C_4H_9ONa	C_2H_5I	f	$C_2H_5CO_2C_4H_9$	(68)	29
	Amides					
12.	*n*-$C_5H_{11}Br$	$(C_2H_5)_2NH$	e,m	*n*-$C_5H_{11}CON(C_2H_5)_2$	80	7
13.	CH_3COCl	$C_6H_5NO_2$	d	$CH_3CONHC_6H_5$	(86)	19
14.	$CH_3(CH_2)_4MgBr$	$C_6H_5NO_2$	d	$CH_3(CH_2)_4CONHC_6H_5$	(68)	19
	α,β-Unsaturated Ketones					
15.	$CH_3(CH_2)_2COCl$		c	 $CH_3(CH_2)_2\overset{O}{\overset{\Vert}{C}}CH{=}CHC_6H_5$	79	20
	α-Diketones					
16.	C_6H_5CHO	C_2H_5I	b	$C_6H_5COCOC_2H_5$	(65)	21
	Aldehydes					
17.	$ClCH_2(CH_2)_5Br$		a	$ClCH_2(CH_2)_5CHO$	82	22,23
18.	$CH_3(CH_2)_2COCl$		a	$CH_5(CH_2)_2CHO$	75	24
19.	$(C_6H_5CO)_2O$			C_6H_5CHO	73	18,25, 26
	Cyclic Ketones					
20.	$Br(CH_2)_2CH{=}CH_2$		p		90	28
21.	$Br(CH_2)_2C(CH_3){=}CH_2$		p		32	28
	Enol Esters					
22.	$C_6H_5COCH_2Cl$	$(CH_3)_2CHCOCl$	o	 $C_6H_5CH_2\overset{OCOCH(CH_3)_2}{\overset{\vert}{C}}{=}CH_2$	79	29
	β-Ketoesters and Nitriles					
23.	*n*-$C_6H_{13}Br$	$CH_2{=}CHCO_2C_2H_5$	n	*n*-$C_6H_{13}COCH_2CH_2CO_2C_2H_5$	92	30
24.	*n*-C_4H_9I	$CH_2{=}C(CH_3)CN$	n	*n*-$C_4H_9COCH_2CH(CH_5)CN$	92	30
25.	$ICH_2(CH_2)_2CH{=}CHCN$		n		82	30

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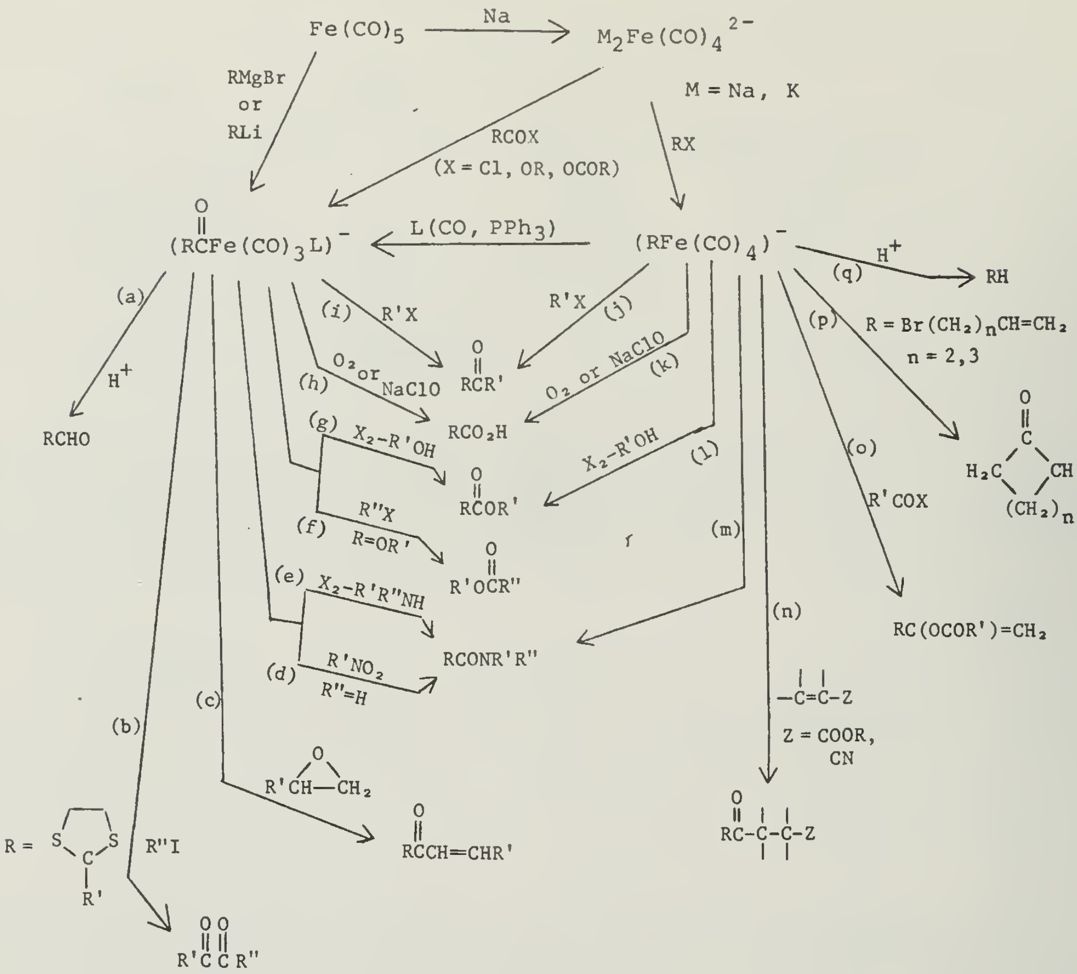
[a] Determined by GLC; isolated yields are in parentheses

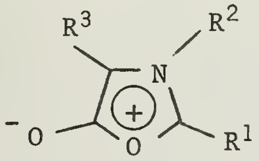
Scheme II. Reactions of Alkyl- and Acyltetracarbonylferrates



Ferrates 1 and 2 have been generated in several ways, some of which were described in Scheme I. $Na_2Fe(CO)_4$ (also $K_2Fe(CO)_4$)[31] has found the most widespread use since, unlike the strongly basic organolithium and Grignard reagents, it is tolerant of several unmasked functional groups including —CN, —COOR, and —CO—. This fact in itself constitutes a major advantage in the use of these preparative methods vis-a-vis classical methods (see reactions 2, 3, 7, and 25 in Table 2). Other advantages include stereospecificity (reaction 1), selectivity (reactions 7 and 17), reagent cost, mild reaction conditions and short reaction periods. Limitations to these methods arise from the basicity of $Na_2Fe(CO)_4$ (approx. equivalent to OH^-)[22] and of the organoferrates. Thus, tertiary substrates cannot be employed and secondary tosylates are preferred over secondary halides. Furthermore, alkylation of 1 and 2 requires reactive primary alkylating agents.

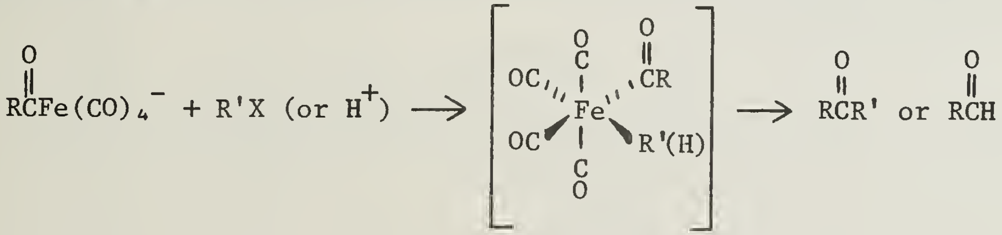
In a typical experimental procedure (such as ketone synthesis) alkyl halide is added to a solution containing a slight excess of $Na_2Fe(CO)_4$ in THF under a nitrogen atmosphere. The reaction mixture is stirred for an hour and a large excess of the second alkyl halide is added. Formation of the acylferrate intermediate can be monitored by infrared spectroscopy. After work-up of mixture with ether and brine the crude product is washed free of colored iron by-products on silica gel and distilled.[4]

Acylferrates have been utilized in several synthetic methods not listed in Scheme II. N,N'-disubstituted ureas are prepared in good yields by the reaction of aromatic and aliphatic nitro compounds with alkyl- and arylcarbamoylferrates, $(RNHCOFe(CO)_4)^-(MgBr)^+$, generated from bromomagnesium amides and iron pentacarbonyl.[32] Cookson[14] has reported that iodoarenes and arylketones are produced by the acylation of lithium acyltetracarbonylferrates with diaryliodonium salts (reaction 5). Esters have been reported to arise from successive reactions of $Na_2Fe(CO)_4$ with aldehydes and alkyl iodides.[33] Collman[14] reported the synthesis of hemifluorinated ketones from perfluoroacid chlorides, anhydrides and pentafluorophenyl iodide. Acylferrates are thought to be intermediates in the direct formylation and acylation of pyradine via pentacarbonyliron.[34] Finally, a new synthesis of mesoionic compounds, 6, (useful intermediates in cycloaddition reactions and precursors of biological compounds including α-amino acid derivatives) involving the reaction of acylferrates with imidoyl chlorides was related by Alper.[35]

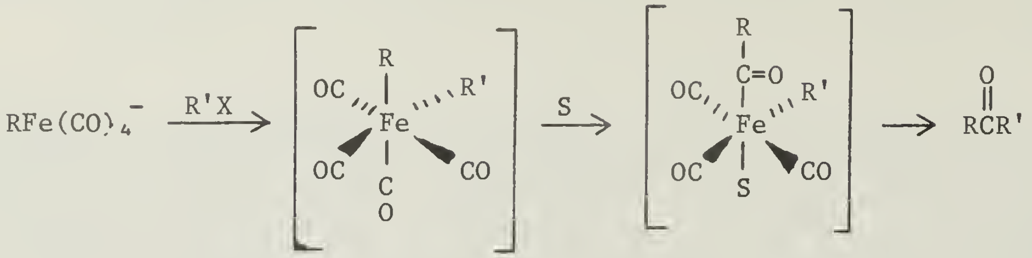


6

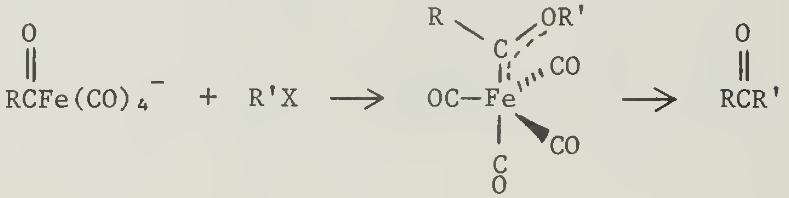
Although the formation of alkyltetracarbonylferrates and/or acyltetracarbonylferrates in the pathways of the synthetic reactions described heretofore has been explained and demonstrated by several workers, the detailed mecahnisms of the subsequent product-forming steps have yet to be elucidated. Nevertheless, some insight into this area has been offered by Collman and others. For instance, the transformation of acylate complex into aldehydes (step a in Scheme II) is thought to proceed through protonation of the iron, affording a six-coordinate iron(II) complex, followed by reductive elimination.[22] The acylketone synthesis (step i), known to follow a second-order rate law, probably occurs by a similar path:



The alkyl ketone synthesis, effected by alkylating the alkyl iron complex (step j), is a second-order reaction. However, it is mechanistically more complex and seems to involve a dialkyl iron complex intermediate though alkyl-alkyl hydrocarbon coupling has not been detected. Such an intermediate would presumably decompose to ketone via the alkyl-acyl iron complex as follows:[4]



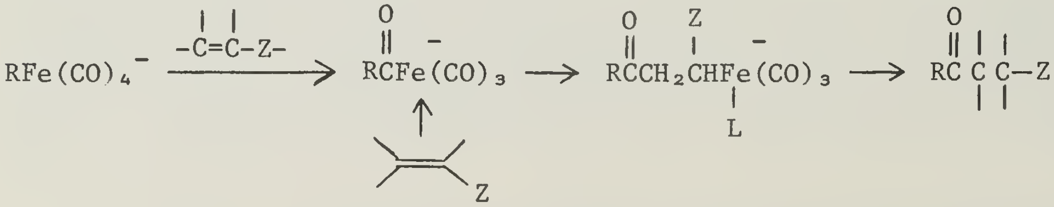
The possibility has been raised[36] that alkylation of the acylferrates occurs at oxygen affording an oxycarbene intermediate as the precursor to ketones.



To demonstrate this is not the case, Collman[25] prepared such a carbene complex (by alkylation of $RCOFe(CO)_4^-$ with $Et_3O^+BF_4^-$) and showed it to be quite stable. Furthermore, Condor and Darensbourg[11] did not detect carbene complex formation in their study of the reaction of acyltetracarbonylferrates with methyl iodide. It is interesting to note that acyloxy carbene complexes are formed by the reaction of ferrate 1 with acid chlorides thereby blocking a potential synthesis of α-diketones.[36]

Halogenation of ferrate 1, yielding esters and amides (step e and g), occurs through an acid halide intermediate. A similar reaction with ferrate 2 (step l and m) is less clear; the halogen serves either to induce migratory insertion or to trap the unsaturated tetracoordinate acyl intermediate 5 proposed in the alkyl-acyl migratory insertion mechanism.[17]

The conversion of organic halides into β-ketoesters, ketones, nitriles and cyclic ketones by means of $Na_2Fe(CO)_4$ (step n and p) is perhaps the most useful synthetic method described in Scheme II. The transformation is believed to proceed via two sequential migratory insertion reactions.[30]



The initial alkyl migration to a metal bound CO affords the acylate complex in which the olefinic acceptor has been incorporated into the coordination sphere of the iron. Preformed acyl ferrate does not subsequently react with added olefin indicating its reluctance to undergo ligand exchange. The initial alkyl migration is followed by the migration of the acyl unit to the terminus of the bound olefin. The coordination vacancy created by this second migration may be filled by either a second olefin molecule (L) or by intramolecular coordination of a functional group within the bound olefin acceptor. The latter alternative is the basis for the cyclic ketone syntheses.[28]

Alkyl- and acyltetracarbonylferrates are potentially very useful transition-metal reagents. While their reactions cannot replace the classical preparative methods, they do provide excellent alternatives in several situations.

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LITHIUM DIORGANOCUPRATES: 1) FUNCTIONALIZED LIGANDS
2) MECHANISM OF CONJUGATE ADDITION TO α,β-UNSATURATED CARBONYL SYSTEMS

Reported by Bruce J. Kokko May 1, 1980

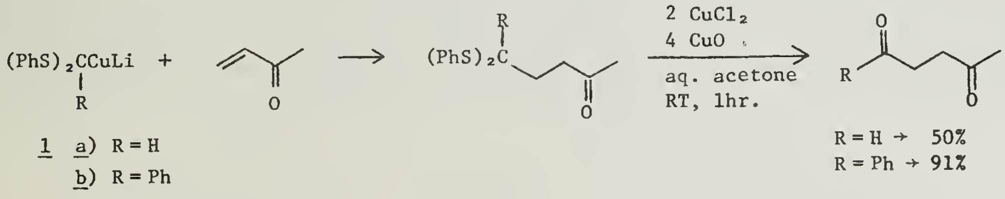
Organocuprates are among the most widely utilized organometallic reagents. They are easy to prepare, give regioselective addition to enones and analogous systems, and undergo a wide variety of substitution reactions with organohalides and epoxides.[1] The gross chemical features of organocuprates have been well established. However, two aspects have remained relatively obscure. These are the use of functionalized ligands, and the mechanism of the conjugate addition of lithium diorganocuprates to α,β-unsaturated carbonyl systems. The topics are discussed herein.

Part I. The Use of Functionalized Ligands. The lithium diorganocuprates are generally prepared by reacting copper(I) salts (usually cuprous halides) with organolithiums. Consequently, the ligands of the organocuprates initially were relatively simple. Recently, functionalized organolithium precursors have been prepared that form active organocuprates. They expand the synthetic utility of organocuprates.

In general, three criteria must be met for the successful preparation of a functionalized copper ligand:[2]

1) The organolithium precursor should be available by a direct route.
2) The organolithium precursor should not be stabilized. Typically, organolithiums that form transferable ligands of copper(I) (*i.e.* ligands that will readily leave the copper atom and bind to the reactive center of a substrate) are hard nucleophiles.
3) If the function to be transferred to a substrate by means of an organocuprate reagent is masked, then the masking group should be removable under a specific set of conditions.

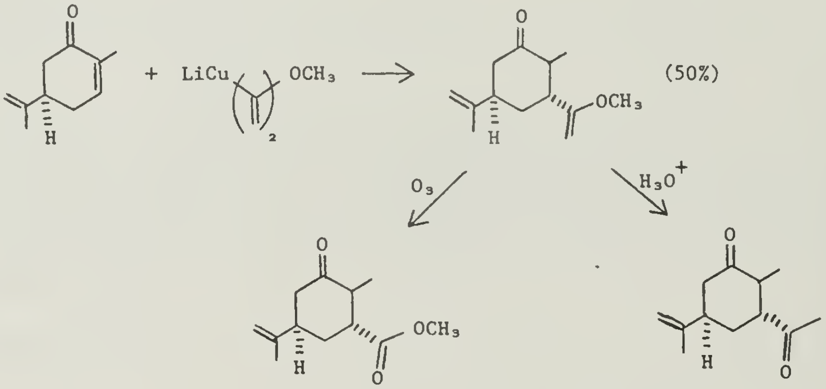
A. The Acyl Anion Equivalents as Transferable Ligands. In 1972, Mukaiyama and co-workers reported that substituted dithiophenylmethylcuprates (1) add to acyclic eneones to give 1,4 adducts.[3] Representative examples of their findings are shown in Eq. 1. These adducts can be easily hydrolyzed to 1,4-dicarbonyl compounds. There is some doubt, however, as to whether Mukaiyama actually prepared the cuprate reagent. It is not clear that this reaction requires the cuprate. Ostrowski reported that acyl anion equivalents give the thermodynamically favored 1,4 adducts without copper catalysis.[4] Indeed, Smith and Manas reported that the reaction of trithiophenylmethyllithium with cyclohexanone, followed by hydrolysis with mercuric salts in methanol, gave 4-carbmethoxycyclohexanone in 95% yield.[5]



(1)

1 a) R = H
b) R = Ph

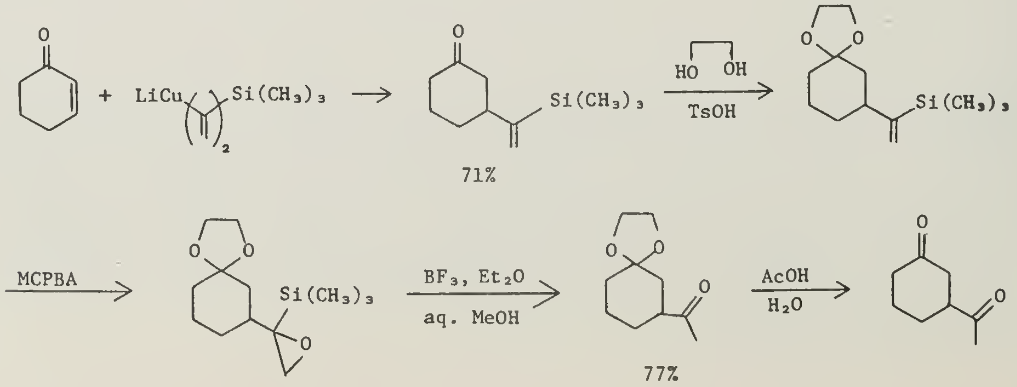
Heathcock and co-workers demonstrated the use of lithium di(α-alkoxyvinyl)cuprates as acyl anion equivalents.[6] They report high yields of 1,4 adducts from the reaction of lithium di(α-methoxyvinyl)cuprate with substituted cyclohexenones. The yields are decreased by substitution in the 2, 3, or 5 positions. Heathcock reports that the 1,4 diketone, or γ-ketoester, can be easily prepared by simple hydrolysis, or ozonolysis, respectively (Eq. 2). In an effort to demonstrate the use of this vinyl cuprate in other reactions typical of organocuprates, they found that lithium di(α-methoxyvinyl)cuprate is alkylated with benzyl bromide, but not with aliphatic halides. Boeckman and workers, using the homologous



(2)

lithium di(α-ethoxyvinyl)cuprate, obtained similar results.[7] These workers report substitutions with allylic halides, but not with epoxides. Boeckman finds that the mixed cuprate with alkynyl ligands has similar reactivity to the aforementioned homocuprate. Consequently, only one equivalent of the α-alkoxyvinyllithium is needed in the preparation of the cuprate. Furthermore, Boeckman has reported that these α-alkoxyvinyl cuprates are not stable above -35°C. Consequently, they cannot be used to add to hindered ketones when temperatures above -10°C are required.[2]

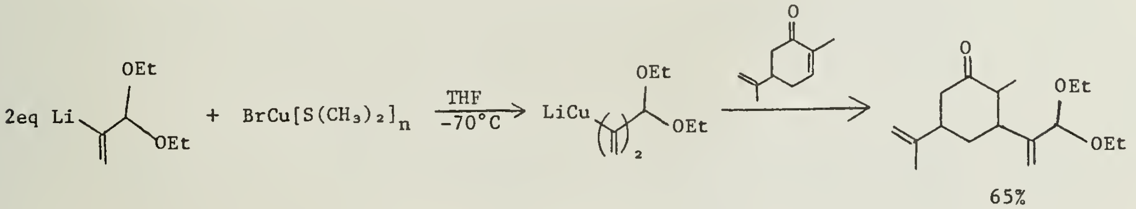
Boeckman has reinvestigated the α-trimethylsilylvinyl ligand.[8] It proved to be more reactive toward hindered enones. This may be attributed, in part, to the increased C-Si bond length. Also, the silylvinyl cuprates are more thermally stable than the α-alkoxyvinyl cuprates. One disadvantage of these ligands is that the demasking procedure requires several steps. A representative sequence is shown in Eq. 3. The requisite vinyllithium is prepared from the α-bromovinylsilane.[9] Analogous reagents can be prepared from the β-bromovinylsilane, and they have been shown to form



(3)

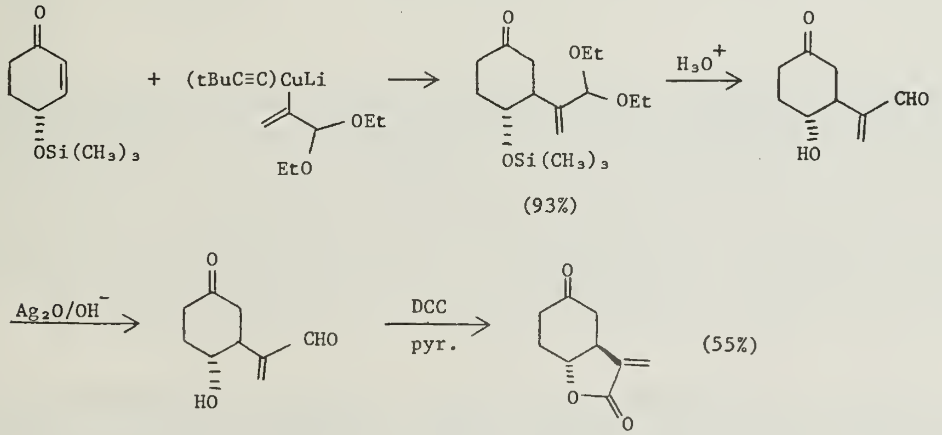
cuprates having reactivity similar to that of the α-vinylsilylcuprates.[8] Such derivatives are excellent enolate equivalents. Substituted α and β-silylvinylcuprates have been prepared and show no marked differences in reactivity with the unsubstituted derivatives.[8] However, they are more sensitive to substitution on the substrate enones.

B. Functionalized 2-Propenyl Ligands. Marino and co-workers reported that lithium α-carbethoxyvinyl(t-butylethynyl)cuprate reacts with allylic halides.[10] The cuprate, however, does not add regioselectively to enones. Marino reported that the functionalized 2-propenyl ligand can be added regioselectively to enones, as propenyl-3-(diethylacetal) (Eq. 4).[11]



(4)

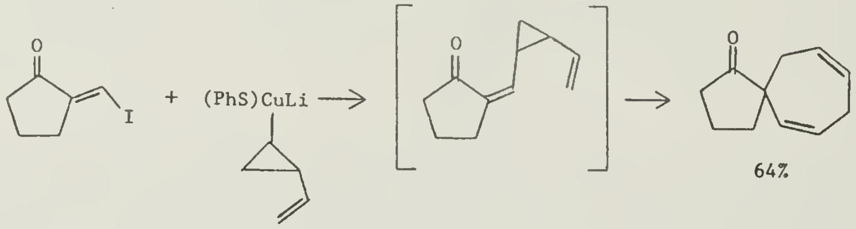
The aldehyde is obtained by hydrolysis with oxalic acid in aqueous acetone. Grieco also reported the use of this ligand in a mixed cuprate with thiophenoxide as a co-ligand.[12] Reaction of these mixed cuprates with enones gives 1,4 addition products in high yields. The cuprates substituted allylic halides, but were reported to be unreactive with alkyl halides and epoxides. Marino reported that the homocuprate added to unsaturated epoxides regioselectively (1,2 ring opening), and gave the trans alcohols in high yields.[13] The regioselectivity is enhanced when the solvent is ether. Boeckman also reported the use of the propenyl-3-(diethylacetal) as the mixed cuprate with t-butylethynyl co-ligand for the preparation of trans-α-methylenebutyrolactones (Eq. 5).[14] Thus, these cuprates are a nice compliment to the existing synthetic methodology for the preparation of trans-butyrolactones.[15]



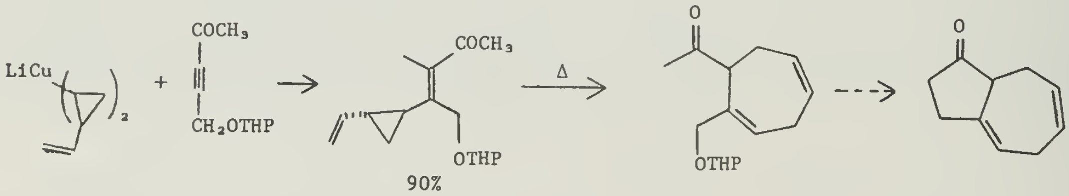
(5)

C. Functionalized Cyclopropyl Ligands. A convenient ring expansion process is the thermolysis of vinylcyclopanes.[16] Because of the synthetic utility of these ring expansions, methods for the preparation of the requisite vinylcyclopropanes have been developed.[17] However, these methods generally lack specificity, or require several steps. Marino and Browne reported the use of lithium dicyclopropylcuprate for the preparation of vinylcyclopropanes.[18] This cuprate was reported to be stable at -40°C, in ether, and it reacts with a variety of β-haloenones and alkynyl ketones to give vinylcyclopropanes in yields ranging from 52-95%. Piers and co-workers reported that lithium cyclopropyl(thiophenoxy)cuprate is more stable than the homocuprate.[19] The reaction of the mixed cuprate with β-iodoenones give the vinylcyclopropanes in high yields.

Marino and co-workers reported that fused and spirocycloheptadienes can be prepared from 1,2-divinylcyclopropanes by a [3,3]-sigmatropic rearrangement.[20] Piers reported that the 1,2-divinyl precursors can be obtained from the reaction of β-iodoenones and lithium(2-vinylcyclopropyl) thiophenoxycuprate.[21] If the temperature is not kept low, the yields of the 1,2-divinylcyclopropane products are low, as they quickly undergo a Cope rearrangement (Eq. 6). Marino and Browne reported a possible route to fused 5- and 7-membered rings, by the reaction of lithium di(2-vinylcyclopropyl)cuprate with the THP ether of 4-oxo-2-pentyn-1-ol.[22] Presumably, the resulting cycloheptadienylmethyl ketone can be cyclized to give the desired fused ring system (Eq. 7). Marino reported that cyclopropylaldehyde is transferred to enones by lithium di(2-diethoxymethylcyclopropyl)cuprate.[22] The aldehyde is obtained by hydrolysis. Piers and co-workers reported the preparation of β-(*endo*-7-norcaranyl) enones from the reaction of lithium(*endo*-7-norcaranyl)thiophenoxycuprate and β-iodoenones.[23] Marino and Browne reported that substitution on the cyclopropane ring does not affect the reactivity of the cuprate.[24] Hiyama and workers reported that substituted cyclopropylcuprates can substitute allylic and alkyl halides in excellent yields.[25]



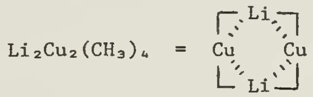
(6)



(7)

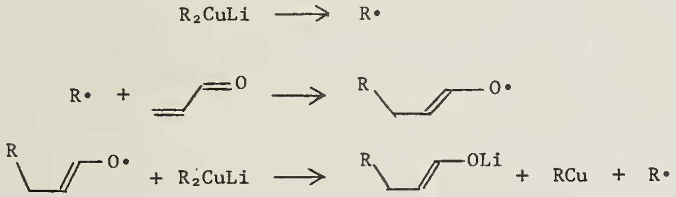
Part II. Mechanism of Conjugate Addition of Diorganocuprates. In this section the model cuprate will be $Li_2Cu_2(CH_3)_4$, and the particular substrate will be specified in the experiments to be examined. The actual structure of lithium dimethylcuprate in ether has been the topic of much speculation. Pearson and Carl performed vapor-pressure depression and X-ray scattering experiments on $[LiCu(CH_3)_2]_n$.[26] Pearson reported that n approximates 2, which suggests a dimer. The Cu-Cu bond length was determined to be 4.4 ± .7 Å, from X-ray scattering data. The methyl groups were determined to be magnetically equivalent by ^{1}H NMR[27] and ^{13}C NMR[28] experiments. Pearson argues that a dimer complex of D_{2h} symmetry and structure shown in Figure 1 is in best agreement with the above data. This structure will be assumed in discussing the mechanism of the conjugate addition of dimethylcuprate to α,β-unsaturated carbonyl systems.

Figure 1



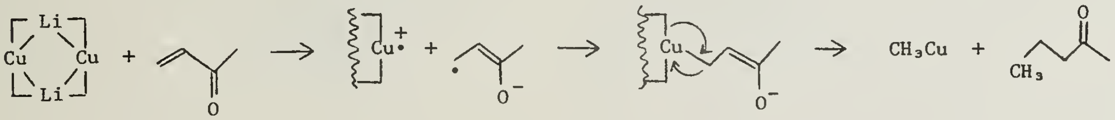
Many mechanisms have been postulated for the 1,4 addition of diorganocuprates to α,β-unsaturated carbonyl systems. It was suggested that conjugate addition by an organocuprate may proceed by a 6-membered transition state.[29] This was ruled out since 1,4 additions to cyclohexenones, where such a transition state is not likely, occur in high yields. The involvement of free radicals has also been considered[30] (Scheme I). However,

Scheme I



Whitesides and Kendall have reported that the reaction of lithium(endo-norbornyl)t-butylcuprate with mesityl oxide leads to the endo-norbornyl ketone.[30] Since no isomerization was observed, the free radical pathway seemed unlikely. Addition of isoprene is reported to have no effect on organocopper reactions.[31]

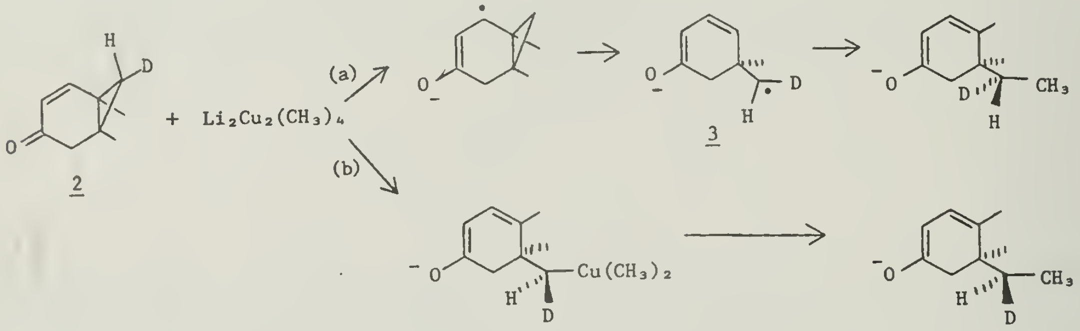
Presently, two mechanisms are under debate. House and co-workers have suggested that the mechanism proceeds via an electron transfer process (Eq. 8).[32] House reported that the susceptibility of enones to

 (8)

to conjugate addition by organocuprates correlates with the reduction potentials of the enones.[32b] Commonly, enones with potentials between -1.4 and -2.35 V (vs SCE in aprotic solvent) gave conjugate addition products. If the enone had a potential more negative than -2.35 V, more poorly reduced, no conjugate addition occurred, and enolate formation was observed. If the enone had a potential greater than -1.4, easily reduced, reduction products were observed. House reported that benzophenone is reduced by $Li_2Cu_2(CH_3)_4$.[32e] However, the use of $Li_2Cu_2(CH_3)_4$ as a reducing agent is not general. House reported that trans-2,2,6,6-tetramethyl-3-heptene-4-one is recovered from the reaction of excess cis-2,2,6,6-

tetramethyl-3-heptene-4-one with $Li_2Cu_2(CH_3)_4$.[32f] House suggests that the isomerization of the starting material may be due to a radical anion intermediate. Ruden and Marshall report ring open products from the reaction of β-cyclopropyl-α,β-unsaturated detones and diorganocuprates, and propose an electron transfer mechanism.[33] The electron transfer process has been questioned, and direct nucleophilic attack by the organocopper complex has been suggested as an alternative pathway. Indeed, substitution of organohalides by organocuprates proceeds with complete inversion of the electrophilic center.[1b]

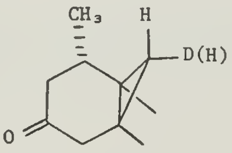
Casey and Cesa studied the reaction of 1,6-dimethylbicyclo[4.1.0]-4-hepten-3-one-exo-7-d_1 (2) with $Li_2Cu_2(CH_3)_4$.[34] Casey suggested an electron transfer pathway and nucleophilic pathway could be differentiated by the degree of stereospecificity in the reaction (Eq. 9). Since there would be



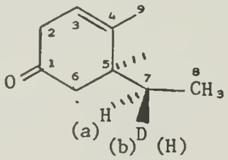
(9)

free rotation of the radical center in the intermediate 3, a mixture of isomers is expected, if the reaction proceeds by the electron transfer pathway (a). However, direct nucleophilic ring opening (b) should proceed stereospecifically. Reaction of 2 with $Li_2Cu_2(CH_3)_4$ gives a 48:52 mixture of the 1,4 adduct 4, and the ring open adduct 5 (Figure 2).

Figure 2



4



5

Adduct 5 is formed stereospecifically. This was determined by analyzing 270 MHZ ^{1}H NMR spectral data. The C-7 methylene protons of the d_0-6 derivative are resolvable as the AB portion of an ABM_3 spin system. The C-7 protons exhibit a quartet of quartets ($J_{ab} = 14.1$ Hz, $J_{aCH_3} = J_{bCH_3} = 7.2$ Hz) in the region between 1.6 and 1.2 ppm. When the C-8 protons are saturated, the C-7 methylene gives an incomplete AB quartet (apparently, the ethyl group is not first order). The diastereotopic C-7 protons are resolvable; however, the chemical shift for each proton was not determined. When the C-8 protons of the d_1 product (5 in Figure 2) are saturated, a singlet at 1.32 ppm is observed with no concomitant resonance for the other diastereotopic proton, so 5 is formed stereospecifically. However, it is not known whether 5 is formed with retention or inversion of configuration. Casey concluded that the opening of the cyclopropyl ring by $Li_2Cu_2(CH_3)_4$ occurs by direct nucleophilic addition of the copper complex to the cyclopropyl ring. This does not rule out an electron transfer mechanism for conjugate addition to enones.

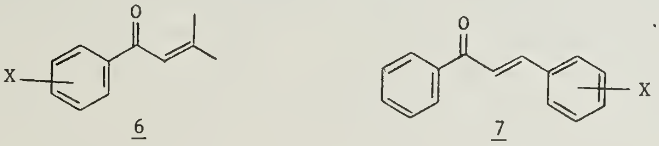
Smith and Krauss are the first to examine the kinetics of conjugate addition of organocuprates to enones.[35] By following the absorbance of an intermediate, formed from the reaction of $Li_2Cu_2(CH_3)_4$ with enones in ether at 25°C, at 380 nm, and plotting the pseudo-first order rate constants for its disappearance verses concentration of cuprate, a rate law and general reaction scheme were derived (Figure 3). From this rate law we see that at low concentrations of cuprate the reaction rate is first order in both enone and cuprate concentrations. However, as the concentration of cuprate is increased, the rate approaches zero order in cuprate (the curve k vs. [cuprate] will flatten out). The degree to which the curve flattens is governed by the magnitude of K (*vide infra*). Smith and Krauss prepared Hammett plots from the data obtained from reactions of substituted 1-phenyl-3-methyl-2-butene-1-ones (6), and β-arylchalcones (7) with $Li_2Cu_2(CH_3)_4$ (Figure 4). The plot of $\log(k_X/k_H)$ vs. σ for the reaction of 6 with $Li_2Cu_2(CH_3)_4$ gives a straight line of slope (p) equal to +1.58. The same plot for the reaction of 7 with cuprate gives a straight line of slope (p) equal to -.88. These data suggest negative charge development on the carbonyl carbon and positive charge development on the β carbon of the enones, in the transition state of the rate determining step. The plots of $\log(K_X/K_H)$ vs. σ, for the reactions of 6 and 7 with $Li_2Cu_2(CH_3)_4$ result in curved lines. For the reaction of 6, the line has a maximum where X = H. For the reaction of 7, the line has a minimum where X = Cl. The interpretation of this data is open to speculation. To address this issue, and the one posed earlier about the effect of K on line shapes, Smith and Krauss compared the rates

Figure 3

$$\frac{-d[Int]}{dt} = \frac{kK[enone][Li_2Cu_2(CH_3)_4]}{1 + K[Li_2Cu_2(CH_3)_4]}$$

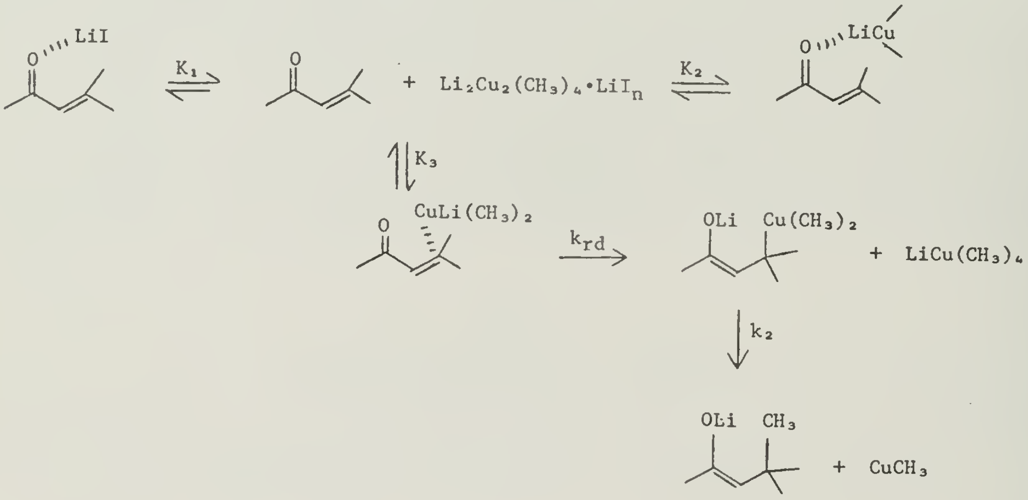
$$Li_2Cu_2(CH_3)_4 \ + \ enone \ \overset{K}{\rightleftharpoons} \ Int \longrightarrow Products$$

Figure 4


6 7

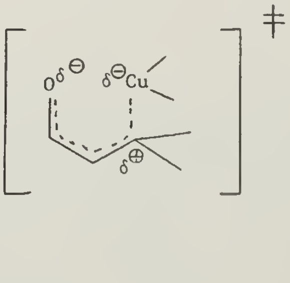
(X = H, p-OPh, $p-CH_3$, p-Cl, and $m-CF_3$)

of reactions of $Li_2Cu_2(CH_3)_4 \cdot LiI_n$ and enones, with the rates of salt-free systems (that is, in the absence of LiI). Smith reports that the salt-free systems give larger rate constants, and the curve generated by plotting the pseudo-first order rate constants vs. concentration of cuprate is more linear. When the reactions of $Li_2Cu_2(CH_3)_4$ and enone, $Li_2Cu_2(CH_3)_4 \cdot LiI_n$ and enone, and LiI and enone were studied by scanning the carbonyl region in IR, broadening of the carbonyl bands was observed in all cases. Smith attributed this broadening to complexation of Li to the carbonyl oxygen.[33a] The Li can either be from the lithium halide or the organocopper complex. Smith postulates the following scheme:



There are many different complexes all in equilibrium, and one or a few are on the reaction pathway. The constant K, in the rate law, is a composite of K_1, K_2, K_3 .... The larger K becomes, the greater is the amount of complexation off the reaction pathway, and the overall rate diminishes. Consequently, the magnitude of K will control the line shape of the curve generated by plotting $k_{(\text{pseudo first order})}$ vs. [cuprate]. The peculiar $\log(K_X/K_H)$ vs. σ plots may be the result of these competitive complexations, especially since the extrema of the curves occurred where X was a mediocre substituent (e.g. Cl can be either electron donating or electron withdrawing). Exact conclusions about these plots are not possible. The $\log(k_X/k_H)$ vs. σ plots suggest a transition state in the rate determining step as shown in Figure 5.

Figure 5



Bonding of the copper to the β carbon of the enone is occurring concomitant with the shift of electron density toward the oxygen. As noted earlier, the overall increase in the rate diminishes with increasing cuprate concentration. If the transition state in Figure 5 is correct for the rate determining step, then as the enone becomes "saturated" with the copper complex, the overall increase in rate relative to cuprate concentration whould approach zero order; since the reaction can only proceed as quickly as bond formation between the copper and the β-carbon of the enone. In light of the above findings, Smith proposes that conjugate addition of $Li_2Cu_2(CH_3)_4$ to the enones studied, proceeds by a nucleophilic addition mechanism. This does not exclude the formation of radical anion intermediates, but the above data, for the systems studied, suggest that the radical anion intermediate is not involved in the rate determining step.

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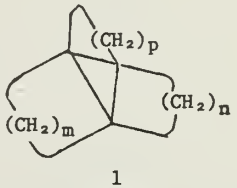
SELECTED ASPECTS OF THE CHEMISTRY OF PROPELLANES

Reported by Sharbil J. Firsan May 5, 1980

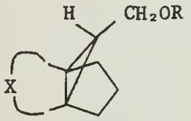
Propellanes, 1, are carbo- or heterocyclic compounds consisting of three rings fused together at a common carbon-carbon bond. The terminology was first suggested by Ginsburg[1] in 1966. Large-ring propellanes ($m, n \geq 4$, $p \geq 2$) behave like "normal" polycyclic aliphatic hydrocarbons[2] and may be formally viewed as hexa-substituted ethanes.[3] However, as m, n, and p become smaller, these molecules become increasingly strained and decreasingly thermally stable.[4] A feature peculiar to the small-ring propellanes ($m, n, p \leq 3$) is the "inverted" tetrahedral geometry around each of the bridgehead carbon atoms.[5] Propellanes were known in the 1930's,[6] but their importance was not realized until the mid-1960's when the first reports of designed syntheses of these species independently appeared from a number of different laboratories.[7]



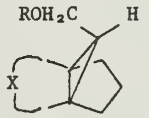
1

Many aspects of propellane chemistry have been adequately reviewed.[8] In recent years, research has focused on four main areas: synthesis (especially of strained systems),[9] theoretical calculations,[3,4] structure-reactivity relationships, and mechanistic/stereochemical studies. These last two aspects will be of direct concern to us in the present report.

Propellanes as Mechanistic/Stereochemical Probes. In an effort to estimate the cycloheptatriene-norcaradiene energy gap, Warner and Lu[10a] studied the solvolysis kinetics of the propellane esters 2 and 3. These were used as conformationally-rigid models for the norcaradienylcarbinyl form in Eq. 1. Using values of k_1 for 2a - d and 3a - d in the rate expression for Eq. 1, the authors were able to calculate K_{eq} and the free energy difference between the tautomers 4 and 5. In light of this and earlier work,[11] they concluded that the anti conformation of 5 is more reactive toward solvolysis than the syn form, and that the energy differ-



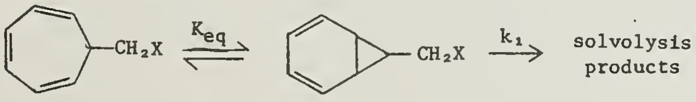
anti
2a - d



syn
3a - d

a, X: $-(CH_2)_2-$; b, X: $-CH{=}CH-$; c, X: $=CH-CH_2-$; d, X: $=CH-CH=$

R = 3,5-dinitrobenzoyl (DNB)

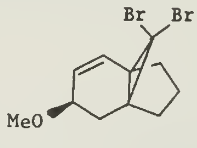


(1)

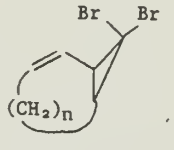
4 5

ence between 4 and 5 is 4 - 4.5 Kcal/mol. Since 4 and 5 provide reasonable models for the parent system, it was inferred that the energy gap between the two tautomers of the parent system should be smaller than the value of 11 ± 4 Kcal/mol originally estimated from a consideration of bond energy terms.[10a]

In another study,[10b] Warner and Chang used the propellane system 6 to probe the mechanism of the known reaction of 7 with methyllithium.



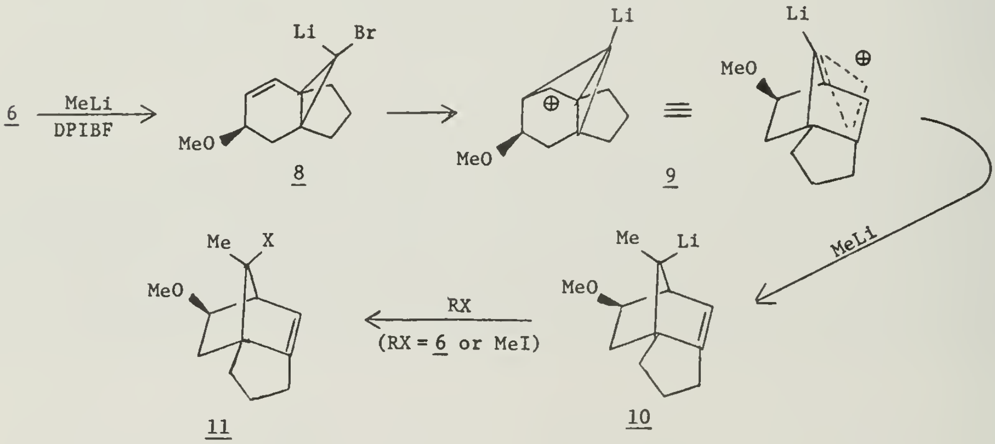
6



7a, b; n = 0, 2

Their results show that no free carbene intermediate is involved in the case of 7, and that the stereoselective conversion of 6 to 11 occurs by a cationic mechanism (Scheme I).

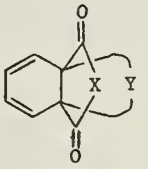
Scheme I



Other studies on propellanes by Warner and co-workers focused on the solvolyses of 9-, 10-, or 11-substituted [n.3.1] and [4.4.1] propellanes,[10c,e,f,g] the stereoselectivity of allylic oxidation with PhSeCl or m-CPBA,[10d] the stereoselectivity of α-hydridocyclopropyl radicals,[10h] and the free-radical bromination of [n.3.1] propellanes in the dark.[10i]

The alkyllithium-promoted cyclization of gem-dihalocyclopropanes to form bicyclobutanes via intramolecular insertion into adjacent C-H bonds is regarded as evidence for cyclopropylidene involvement.[12] In order to investigate the discriminatory properties of cyclopropylidenes in their C-H insertion reactions, Paquette and co-workers[12a] have incorporated the carbenoid center into a [m.n.1] propellane framework. Their results show the regiosepcificity of the insertion reaction to be dependent upon the relative proximity and nucleophilicity of the adjoining axial C-H bonds, and permit the ordering of these bonds on the basis of their relative reactivity toward carbenoid insertion.

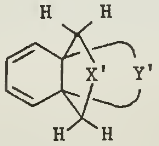
Structure-Reactivity Studies. Ginsburg and co-workers have studied the reactions of unsaturated propellanes with dienophiles[13] and electrophiles[14] in order to elucidate those structural features that control the stereochemistry of the addition. In the [4.4.3] and [4.4.2] propelladiene, triene, and tetraene systems,[13e,g,j,k,m,n,o] they identified two distinct structural types, 12 and 13, that have opposite directive effects towards the incoming 4-substituted-1,2,4-triazoline-3,5-diones 14.[13g] Secondary orbital interactions between the carbonyl π^* orbitals in 12 and the n_- combination of the lone-pairs orbitals in 14 stabilize the transition state of syn attack relative to that of anti attack, thus resulting in exclusive formation of the syn Diels-Alder mono-adduct. The absence of such a favorable electronic interaction, and the presence of repulsive steric interactions with the hydrogen atoms of the bridge in the transition state of the syn attack in 13, results in exclusive formation of the anti Diels-Alder mono-adduct. However, the second equivalent of dienophile adds from the side syn to the bridge to give a symmetrical and an unsymmetrical bis-adduct from 12 and 13, respectively. This is believed to be due to the steric hindrance to anti attack exerted by the boat conformation of the mono-adduct.



12

Y: $=CH-CH=$, $-CH=CH-$, $=CH-CH_2-$, $-(CH_2)_2-$

X: O, NH, NMe, NPh

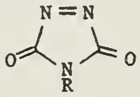


13

Y': $=CH-CH=$, $-CH=CH-$, $=CH-CH_2-$, $-(CH_2)_2-$

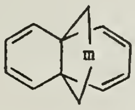
X': O, CH_2, S, NH_2^+

Y': $=CH-CH=$, $-(CH_2)_2-$; X' = zero



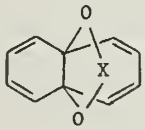
14a, R = Me
b, R = Ph

[4.4.3] Propellatetraenes 15 and 16a,b and the [4.4.2] propellenes 17 were found to behave analogously to 13.[13g,j,k,m] Contrary to what was expected, the transition state for syn approach is destabilized due to repulsive interactions between the n_+ orbital combination in 14 and the filled π orbital of the cyclobutene carbon-carbon double bond in 17, or the filled lone-pair orbitals on O, S, or NR in 15 or 16a,b. Bis-adduct formation is not observed for 16c.



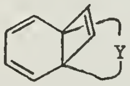
15

m: O, S, NR



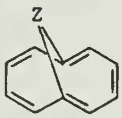
16a - c

a, X: CH_2; b, X: CO, c, X: CMe_2



17

Y: $=CH-CH=$, $-(CH_2)_2-$

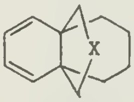


18

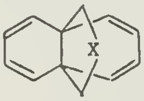
Z: CH_2, O, NH, NMe

The directive influence of centrally-located hydrogen atoms or lone-pair orbitals above the reaction site, as in 18 (note: bridged [10] annulenes are "open" [4.4.1] propellenes), was also investigated.[13f,h,l] It was found that both the first and the second equivalent of dienophile add from the side opposite to the bridging group. Probably, the steric and electronic repulsive interference from the Z group overrides the steric hindrance of the boat conformation in the mono-adduct.

The effect of a polar group as in thiapropelladienes 19 and thiapropellatetraenes 20 (both formally of type 13 or 15) was studied.[13j]

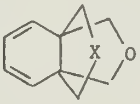


19a - c



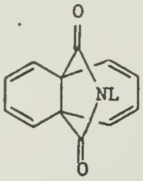
20a - c

a, X = S; b, X = SO; c, X = SO_2



21, X = SO

22, X = SO_2



23a - c

a, L = Ph; b, L = 2,6-dimethylphenyl; c, L = neopentyl

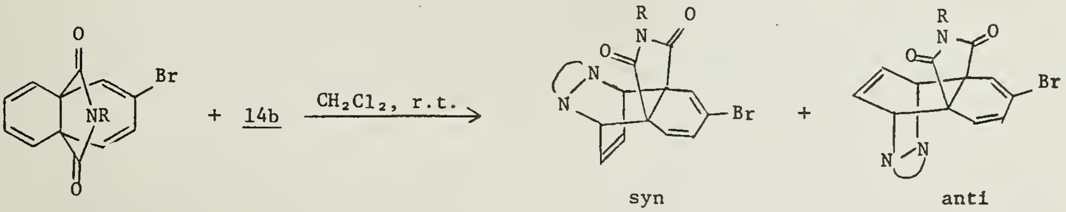
All the mono-adducts of 19 are formed by exclusive syn attack. However, 20a gives exclusive anti attack, 20c mainly syn, and 20b a complex mixture of mono- and bis-adducts. Electrostatic potential field MO calculations[8j] carried out on 20c and 14 indicated that the preference for syn approach in this case could arise from two favorable electrostatic interactions: one between the positively polarized sulfur atom and the nitrogens lone-pairs, and the other between the negatively polarized oxygen atoms and the positive electrostatic field on either side of the triazolinedione ring.

The mono-adducts of 21 and 22 are formed by preferential syn (to the thioether ring) addition of the triazolinedione.[13e,j] This observation agrees with PMO theory predictions that the closeness in energy of the n_+ combination of the lone-pairs in 14 to the 2P lone-pair orbital on oxygen in 21 and 22 would make approach from the thioether ring side a less energetically disfavored process than approach from the ether side.

Cases where steric interference with secondary orbital overlap would be expected, as in 23, to result in bis-anti addition (in analogy with 18) were considered.[8d,13h,k] Like 12, upon treatment with the dienophile 14, 23a gives a quantitative yield of the syn adduct.[13h] Both 23b and 23c, however, give a 1:1 mixture of the two isomeric mono-adducts. The possibility of free rotation around the N-C bond in 23a but not in 23b,c is invoked to explain these observations.

Further support for the secondary orbital control hypothesis comes from the observation that addition syn to the heterocyclic ring in 12 (Y: =CH-CH-, $-(CH_2)_2-$; X: NCH_3) results when singlet oxygen[13c] is used as the dienohpile, whereas exlusive anti addition to 12 (Y: =CH-CH=, X: O) occurs when N-phenylmaleimide (24) or p-benzoquinone (25) is the dienophilic component.[13a] These results agree with the observation that the HOMO of $^1O_2$ is of the π^*-type and is thus capable of overlapping with the vacant π^* orbitals of the carbonyl groups in 12. No such interaction is possible in the case of 24 or 25, and steric factors arising from the hydrogen atoms of the carbon-carbon double bond dictate the stereochemistry of addition.

In most of the cases considered thus far, the symmetry of the substrates precludes any examination of the regiochemistry of the [4 + 2] cycloaddition. Ginsburg, Vogel, and co-workers addressed this question by reacting the unsymmetrical propellatetraenes 26a,b with 14b.[13b] The mono-adducts formed result from the addition of the dienophile to the unsubstituted diene system (Eq. 2). Addition of a second equivalent of 14b to 27 and 28 occurs syn to the original imide ring to give the respective bis-adducts.

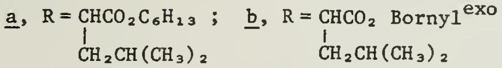


(2)

26a,b

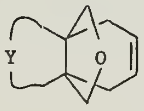
27a (18%)
b (25%)

28a (43%)
b (45%)

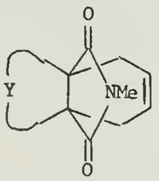


$$\text{a, } R = \underset{\displaystyle CH_2CH(CH_3)_2}{CHCO_2C_6H_{13}}\ ;\quad \text{b, } R = \underset{\displaystyle CH_2CH(CH_3)_2}{CHCO_2}\ \text{Bornyl}^{exo}$$

Ginsburg and co-workers[14] also looked at the attack of the double bond(s) by electrophiles. Addition of m-CPBA to propellenes 29 gives inter alia a 1:1 mixture of syn and anti mono-epoxides, but a 6:1 and a 2:1 mixture with 30a and 30b, respectively.[14d] The preference for syn addition seen for 30 but not for 29 is attributed to secondary orbital interactions between the incoming peracid NHOMO and the π* orbitals of the carbonyl groups, assuming a concerted mechanism for the epoxidation reaction.



29a,b

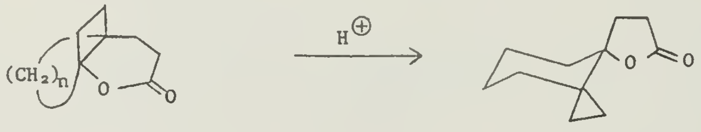


30a,b

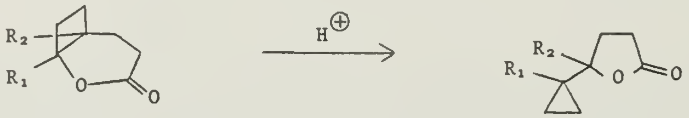
a, Y: -CH=CH-; b, Y: $-(CH_2)_2-$

Low configurational selectivity and poor yields are observed in the addition of nitrenes to 29a and 30a.[14c] However, carbethoxycarbene gives preferential attack anti to the imide ring in 30.[14a,b] This preference is due to the fact that 30a,b exist in the exo-exo boat conformation in solution; syn addition of the carbenoid would result in a highly sterically congested structure.

In another series of studies, the effect of the size of the "third" ring on the reactivity of propellanes in a number of different reactions has been investigated.[15] One such reaction is the acid-catalyzed,[15g] or the thermally-induced[15a] cyclobutyl-cyclopropylcarbinyl rearrangement. When Odaira and co-workers[15g] treated the δ-lactones 31 and 33 with acid, only 31b and 33d,e were converted to the corresponding γ-lactones (Eqs. 3 and 4). Moreover, heating of 31a-d and 33a-e in a sealed tube at 240°C for 72h or at 350°C for 20 seconds in a nitrogen stream gives quantitative yields of the γ-lactones 32a-d and 34d,e.[15a] On the basis of what is known about the mechanism of the acid-catalyzed cyclobutyl-cyclopropylcarbinyl rearrangement in other systems, and the observation that the corresponding thermal process is reversible for the cases considered, the authors claim that the δ-lactones 31 and 33 are converted to the γ-lactones 32 and 34 by a stepwise, cationic mechanism under acid-catalysis, and by a concerted, disrotatory ring-opening in the thermal process. The differences in reactivity of the δ-lactones in either process are attributed to conformational changes in the cyclobutane ring undergoing the reaction. The steric interaction between the 1,2-dialkyl substituents in 33d,e and the tendency of the cyclohexane ring in 31b to adopt a chair conformation force the cyclobutane rings in the corresponding cationic intermediates 35, or the transition state for the thermal process to have a more puckered geometry. This allows for better orbital overlap in 35 and for an antiperiplanar arrangement of the two migrating bonds in 36, and facilitates the rearrangement in either case.

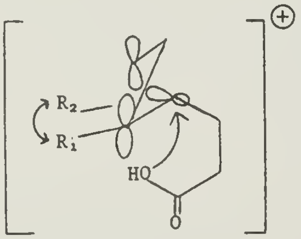


31a - d, n = 3 - 6 32 (3)



33a,e 34d,e (4)

a, $R_1 = R_2 = H$; b, $R_1 = CH_3$, $R_2 = H$; c, $R_1 = H$, $R_2 = CH_3$;
d, $R_1 = R_2 = CH_3$; e, $R_1 = C_2H_5$, $R_2 = CH_3$



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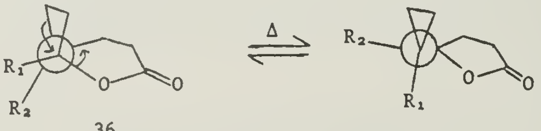
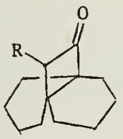


36 37

The effect of the size of the "third" ring on the course of the photochemical reaction (ring expansion *vs.* cycloelimination *vs.* decarbonylation) of a cyclobutanone moiety incorporated in a propellane was also demonstrated. Odaira and co-workers[15b] showed that propellanones 38 but not 40 photodimerize in pentane *via* an oxacarbene intermediate 39. The steric constraints and ring strain in the propellanone are believed



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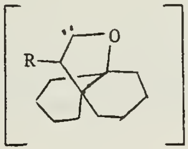

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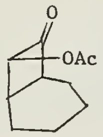

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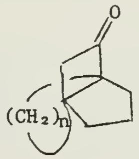
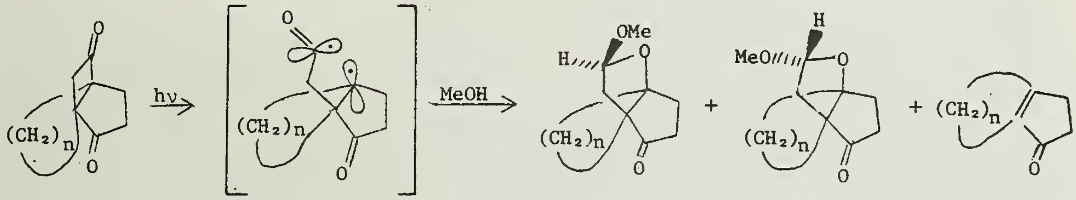


41a - d, n = 3 - 6

a, R = OAc; b, R = $OCOC_2H_5$

to cause irreversible ring expansion to afford 39 that undergoes dimerization. When the photoreaction is run in methanol (Eq. 5),[15c] the results with 41 and 42 show that the extent of cycloelimination and the syn/anti



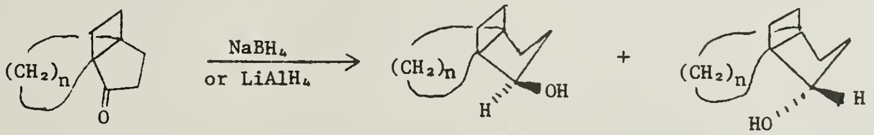
(5)

42 43 44 (syn) 45 (anti) 46

a, n = 3; b, n =4; c, n = 5; d, n = 6

ratio increase with an increase in the size of the "third" ring. The formation of the syn ring-expansion acetal was favored regardless of the "third" ring size, and a change in the latter has a greater effect on the photochemical process than on the syn/anti ratio. This effect on the course of the reaction cannot be attributed to a *steric* effect originating from the conformational flexibility of the "third" ring (*vide infra*), but rather to the degree of rigidity or flexibility of a bridgehead radical in a singlet biradical 43. On the contrary, the *steric* hindrance to approach of methanol to the oxacarbene intermedaite from the "third" ring side (due to the conformational flexibility of the latter) plays a key role in determining the syn/anti ratio of the ring-expansion acetals.

The product stereochemistry in the metal hydride reduction of [n.3.2] propellanones[15f] is sensitive to "third" ring size (Eq. 6). The exo/endo ratio of the product alcohols increases gradually as n increases from 3 to 6. This indicates that the non-bonded interaction in the transition state for hydride approach from the endo side of 47 are less than those



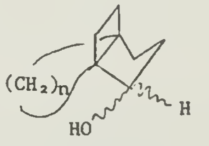
(6)

47 exo 48 endo 49

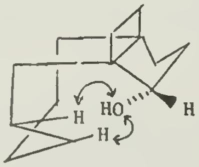
a, n = 3; b, n = 4; c, n = 5; d, n = 6

for approach from the exo side. This is attributable to the greater conformational flexibility of the "third" ring as compared to that of the cyclobutane ring in 47.

A study of the rate of chromic acid oxidation of [n.3.2] propellanols 50 shows that the relative rate constants in the exo series increase only slightly, but that those in the endo series increase remarkably with "third" ring size.[15e] These results together with the known acceleration of the oxidation rates due to the relief of non-bonded interactions in going from the ground state to the transition state suggest that the large increase seen for the endo alcohols reflects the fact that as n increases, the conformational flexibility of the "third" ring increases. In turn, the non-bonded interactions between the endo hydroxyl group and the hydrogens of the ring increase in the ground state, *e.g.*, 51. This is not the case for the exo alcohols, since the hydroxyl group is located on the opposite side of the "third" ring and at the outside of the envelope of the cyclopentane ring.

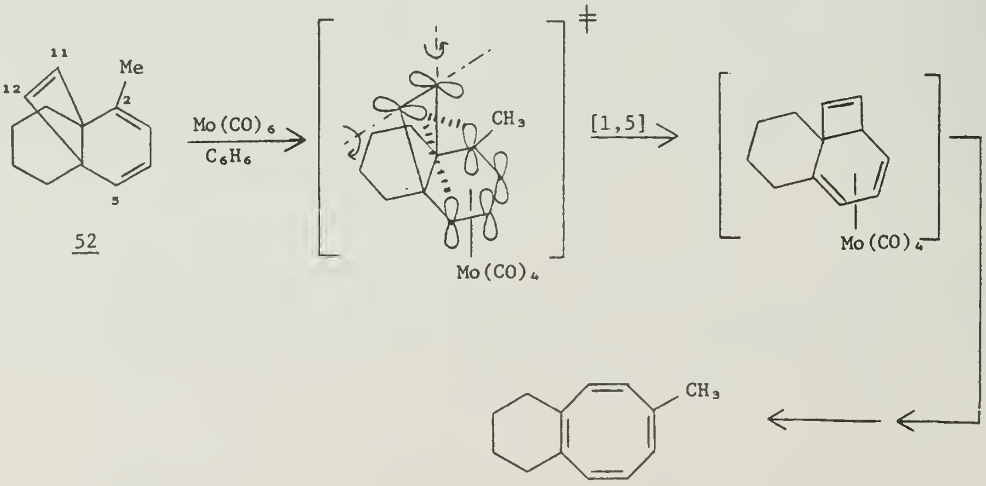


50a - d, n = 3 - 6



51

Finally, Paquette and co-workers[16] have found that $Mo(CO)_6$ uniquely catalyzes isomerization of [4.4.2] propelladienes and trienes to 1,2-annulated cyclooctatetraenes (Eq. 7). This process requires a 1,3-cyclohexadiene unit laterally fused to a strained four-membered ring,



52

53

(7)

and occurs by a different mechanism and under milder conditions than the thermal one. The [1,5] sigmatropic migration occurs within the "coordination sphere" of the metal that is temporarily complexed to the underside of the propellene system. Mono-substitution at C-11 or C-12 results in regiospecific migration of the unsubstituted carbon center, whereas substitution at C-2 or C-5 results in regioselective migration towards the substituent. When both C-11 and C-12 are substituted, double bond-shift isomerism as well as extended circumambulation are observed.

Conclusion. The unique structure of propellanes makes them suitable targets for structure-reactivity as well as mechanistic studies. It also allows the observation of novel and facile skeletal rearrangements in these systems.

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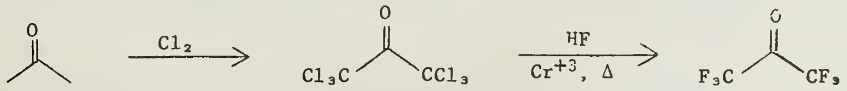
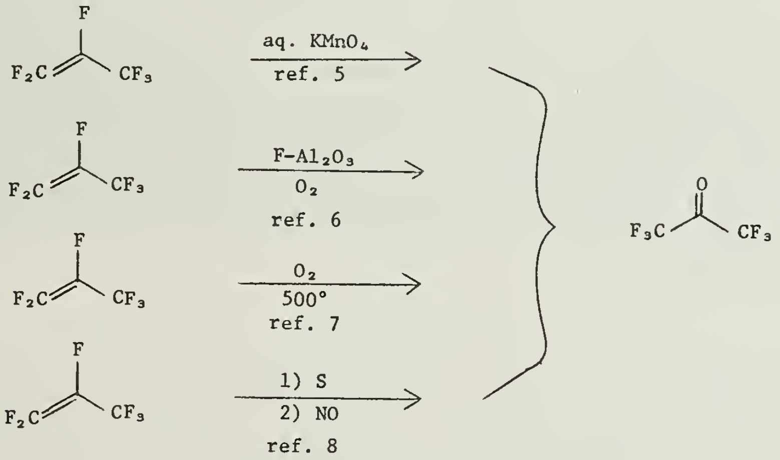
THE CHEMISTRY OF HEXAFLUOROACETONE

Reported by Eugene P. Janulis May 8, 1980

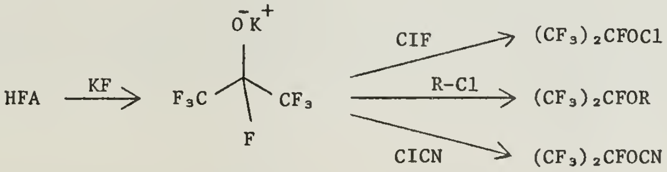
Hexafluoroacetone (HFA) is a reactive, gaseous (b.p.$^{-}$27.28°)[1] perfluoroketone. It was first isolated in 1941, in low yield, as one of several products obtained from the direct fluorination of acetone.[2] Industrially, HFA is currently prepared from the fluorination of hexachloroacetone by hydrogen fluoride and a chromium catalyst.[3,4]



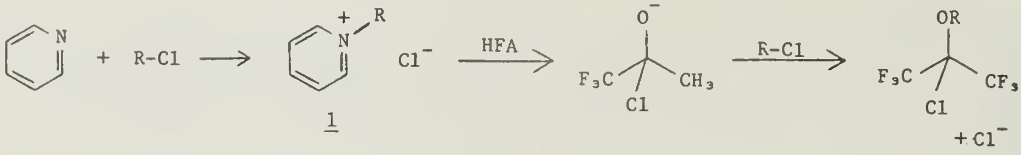
Today there are several alternative routes to HFA, some of which can be used for easy preparation of HFA for the laboratory.[5-8]

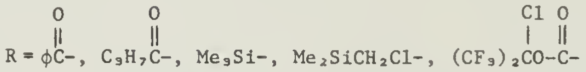


HFA's chemical properties differ markedly from those of other ketones. The opposing inductive effects of the trifluoromethyl groups result in the low polarity and exceptional electrophilic character of the carbonyl group. As a consequence, HFA is resistant to attack by electrophilic reagents.[9] However, as would be expected, the carbonyl group is very susceptible to attack by nucleophilic reagents and this is the basis for much of the chemistry of HFA.[10,11] HFA and alkali metal or silver fluroides react to give salts of 1,1,1,2,3,3,3-heptafluoro-2-propanol.[12,13]



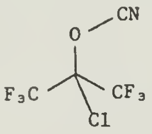
These salts have been used to prepare a variety of compounds, many of which result in the net nucleophilic addition of a normally electrophilic reagent to HFA.[14-21] Another method for net nucleophilic addition of an electrophilic reagent to HFA is the reaction of alkyl, acyl, and silyl chlorides with HFA in the presence of pyridine.[22,23] The mechanism is





$$R = \phi\overset{\overset{O}{\|}}{C}-,\ C_3H_7\overset{\overset{O}{\|}}{C}-,\ Me_3Si-,\ Me_2SiCH_2Cl-,\ (CF_3)_2\overset{\overset{Cl}{|}}{C}O-\overset{\overset{O}{\|}}{C}-$$

believed to involve initial formation of the pyridinium salt, 1, followed by nucleophilic attack of the chloride ion to HFA. This α-chloroalkoxide anion intermediate can then react with either alkyl chloride or pyridinium salt to give the product, which results in the net addition of R-Cl across the carbonyl of HFA. The fact that in the presence of benzyltriethylammonium chloride, $C_6H_5CH_2N^+(CH_2CH_3)_3Cl^-$, reaction occurs, but at a rate slower than that when pyridine is used, and that no reaction takes place in the absence of catalyst, supports this type of mechanism.[24] Also, it has been observed that in the presence of pyridine the rate of addition of trimethylsilylazide to HFA is enhanced. However, it is interesting to note that the reaction of HFA and cyanogen chloride in the presence of pyridine does not give the cyanate, 2, but rather the dioxazine, 3. What is believed to occur here is initial addition of pyridine to cyanogen chloride, forming the zwitterionic intermediate, 4, which adds nucleophilically to HFA.



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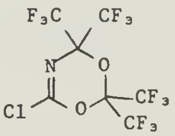

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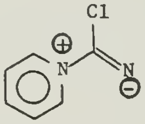
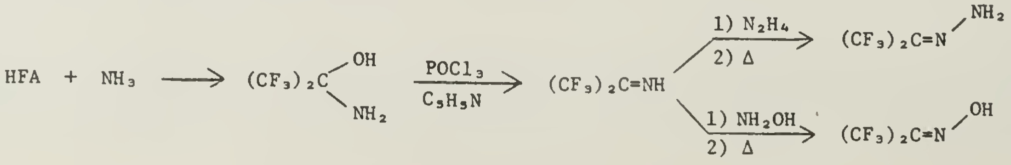


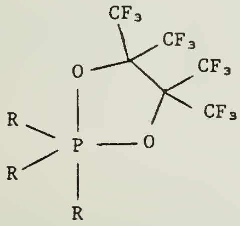
4

Reactions with Amines. Amines add across the carbonyl group of HFA in an exothermic reaction to give stable *gem*-aminoalcohols. Thermal dissociation to the imine does not occur. Dehydration is accomplished with phosphorous oxychloride in the presence of pyridine.[24] Hydrazine behaves as a diamine and reacts with two equivalents of HFA and gives hexafluoroacetoneazine upon dehydration.[25] Thus, the hydrazone, and also the oxime, of HFA cannot be prepared in the usual manner. Synthesis of the hydrazone and the oxime is accomplished by thermal elimination of ammonia from the adducts obtained from the reaction of HFA-imine with hydrazine or hydroxylamine.[24,26] The hydrazone is converted to bis(trifluoromethyl)diazomethane



with lead tetraacetate.[27] The oxime has found wide use as a solvent for many polyamide and polyester polymers.[28]

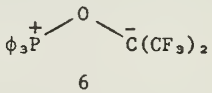
Reactions with Phosphorous Compounds. Unlike the reactions of HFA with amines, HFA's reactions with phosphorous compounds are more varied and far less understood mechanistically. The reaction of HFA with triethylphosphite gives the 1,3,2-dioxaphospholane 5a.[29] Two reaction mechanisms were postulated to account for the observed product: (1) a concerted cyclization and (2) the intermediacy of a three-membered, cyclic, 1:1 adduct of HFA and triethylphosphite. Ramirez[30] and Stockel[31] found that triphenylphosphine and HFA gives the phosphorane 5b. Stockel proposed the intermediacy of the zwitterionic species 6, generated from the nucleophilic addition of phosphorous to the carbonyl oxygen of HFA. Attempts to trap 6 using dimethylacetylenedicarboxylate proved unsuccessful.[31] The reaction of trialkylphosphines with HFA gives the phosphorane 5c, which rearranges on warming above 80° to the phosphorane 7. Above 120° 7 decomposes to the 1,1-bis(trifluoromethyl)alkene.[32,33]



5a ($R = OC_2H_5$)

5b ($R = C_6H_5$)

5c ($R = CH_3$, C_2H_5)



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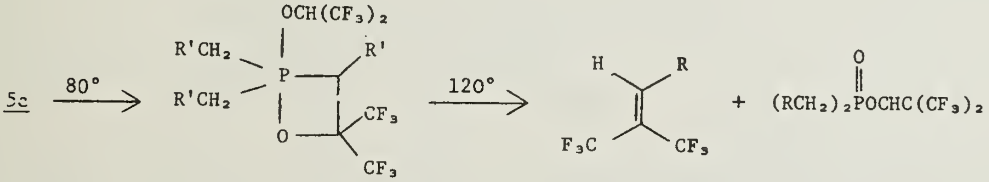
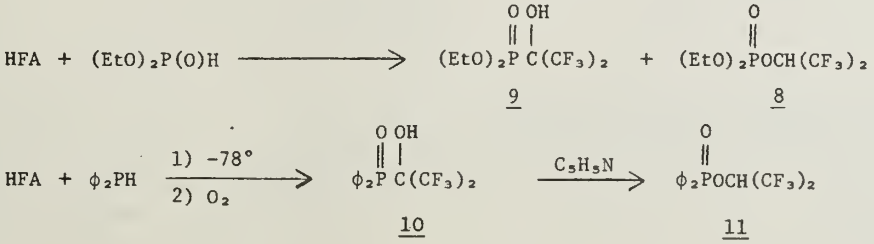


7

R' = H, Me

HFA reacts with $(EtO)_2P(O)H$ at 50° to give the phosphate 8.[34] Janzen, however, found that at lower temperature not only 8, but also the phosphonic diester 9, is formed, which rearranges to 8 in the presence of an amine base.[35,36] Janzen[37] and Ramirez[38] both found that diphenylphosphine gives the phosphine oxide 10 after reaction with O_2 or N_2O_4. Addition of base effects rearrangemet of 10 to 11. Finally, reaction of diethyltri-

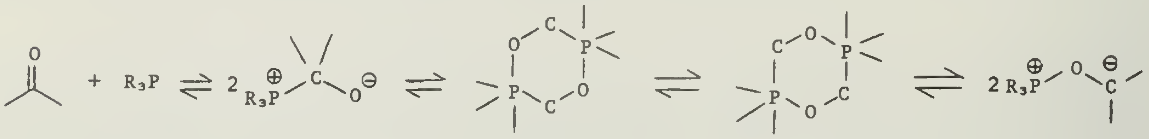


$$\mathrm{HFA} + (\mathrm{EtO})_2\mathrm{P(O)H} \longrightarrow \underset{\underline{9}}{(\mathrm{EtO})_2\overset{\mathrm{O}}{\overset{\|}{\mathrm{P}}}\,\overset{\mathrm{OH}}{\overset{|}{\mathrm{C}}}(\mathrm{CF}_3)_2} + \underset{\underline{8}}{(\mathrm{EtO})_2\overset{\mathrm{O}}{\overset{\|}{\mathrm{P}}}\mathrm{OCH}(\mathrm{CF}_3)_2}$$

$$\mathrm{HFA} + \phi_2\mathrm{PH} \xrightarrow[\text{2) } \mathrm{O}_2]{\text{1) } -78^\circ} \underset{\underline{10}}{\phi_2\overset{\mathrm{O}}{\overset{\|}{\mathrm{P}}}\,\overset{\mathrm{OH}}{\overset{|}{\mathrm{C}}}(\mathrm{CF}_3)_2} \xrightarrow{\mathrm{C_5H_5N}} \underset{\underline{11}}{\phi_2\overset{\mathrm{O}}{\overset{\|}{\mathrm{P}}}\mathrm{OCH}(\mathrm{CF}_3)_2}$$

methylsilylphosphite affords the compound in which the trimethylsilyl group has migrated to the carbonyl oxygen of HFA.[39,40] Based on these observations Ramirez proposed a new mechanism, outlined in Scheme I, to account for these new results.[39] The bimolecular intermediate 12 can undergo pseudorotation to 13. And the last equilibrium involving 13 can occur only if the resulting negative charge can be accommodated by the presence of strongly electron-withdrawing substituents, such as the two trifluoromethyl groups in HFA.

Scheme I



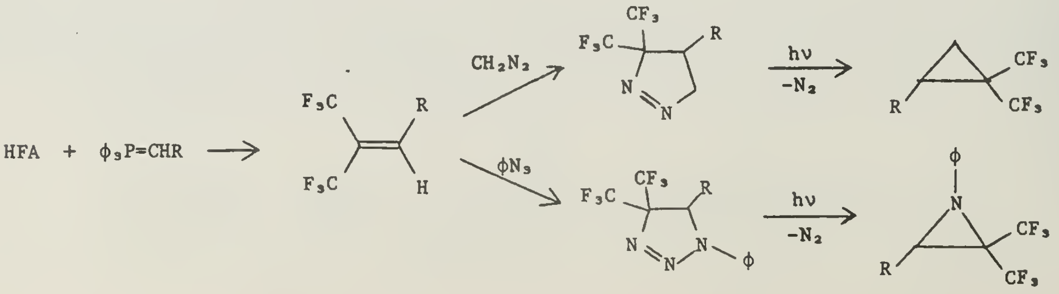
12 13

An alternative mechanism not considered in the literature involves electron transfer. As Ramirez noted, compounds to which trivalent phosphorous "adds" to the oxygen of a carbonyl include HFA, quinones and cyclopentadienones.[41] HFA has a half-wave potential of -0.8 volts.[42] MNDDO calculations give an estimated electron affinity of ca. 50 kcal/mol for HFA. The charge and spin densities of HFA radical anion calculated by MNDDO and INDO are given in Table 1.[43]

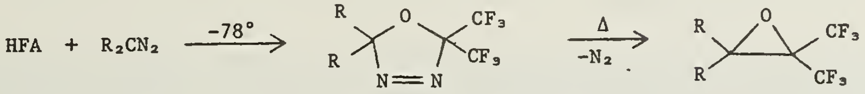
Table 1. Charge and Spin Densities for HFA$^{\dot{-}}$

	Charge		Spin	
Atom	MNDDO	INDO	MNDDO	INDO
Carbonyl O	-0.42	-0.37	0.45	0.61
Carbonyl C	-0.32	-0.24	0.53	0.33

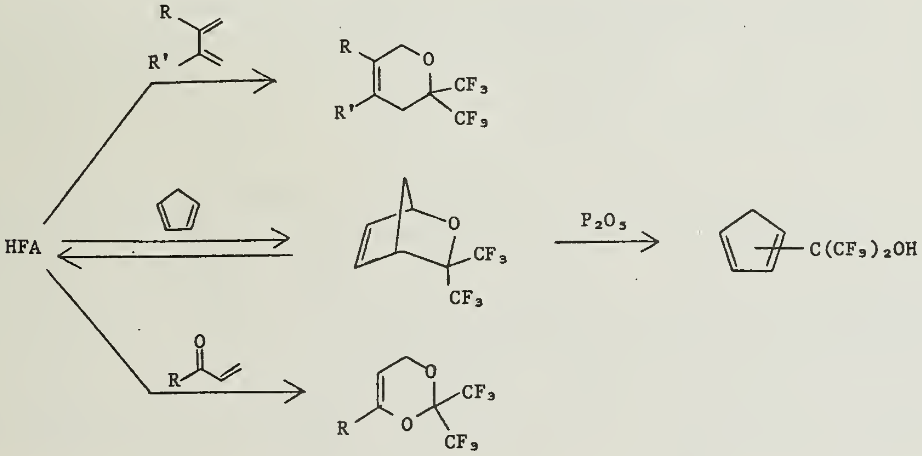
Reaction of HFA with Wittig reagents, even normally unreactive ones, gives olefinic products.[44-46] Reactions of these olefins with diazomethane or aryl azides affords the corresponding di- or triazolidine. Photolysis of these azolidines gives a novel synthetic route to 1,1-bis(trifluoromethyl)-2-substituted cyclopropanes and 1-aryl-2,2-bis(trifluoromethyl)-3-substituted aziridines.[46]



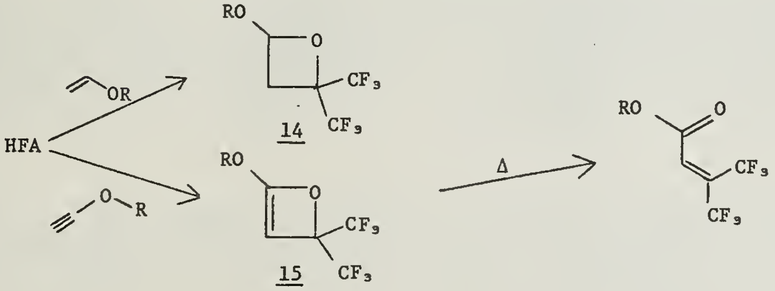
Reactions with Unsaturated Compounds. HFA also reacts with aryldiazomethanes to give 1,3,4-oxadiazolines which decompose on warming to α,α-bis(trifluoromethyl)-β,β-diaryloxiranes.[47] HFA reacts with olefins



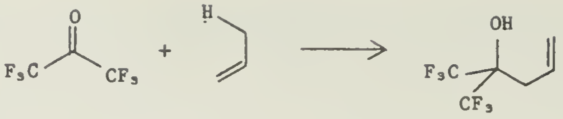
to give a variety of products dependent on type of olefin substitution and degree of unsaturation. HFA reacts with ketenes affording β-lactones. Upon warming the lactones decompose providing an interesting route to 1,1-bis(trifluoromethyl)-2,2-disubstituted ethylenes.[48,49] HFA is a potent dienophile, reacting with dienes and α,β-unsaturated carbonyls giving the [2+4] cycloadducts.[50-53] The cyclopentadiene-HFA adduct



is unstable but can be isolated as the dibromide.[52] HFA reacts with vinyl ethers to give stable oxetanes, 14,[54,55] and acetylenic ethers react with HFA to give oxetes, 15, which slowly rearrange at room temperature



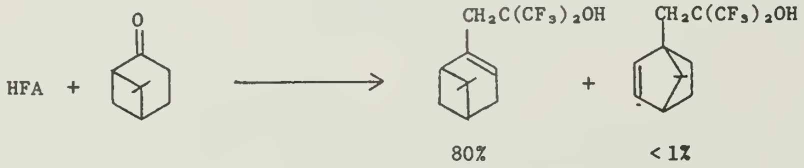
to unsaturated esters.[56] HFA reacts with alkenes containing an allylic hydrogen in a manner reminiscent of the ene reaction of singlet dioxygen with allylic olefins.[54,57-59] Although terminal olefins are the most reactive, internal olefins also react, especially in the presence of a Lewis acid catalyst.[60] There has been debate whether the mechanism is a stepwise or a concerted process. Adelman has observed an appreciable



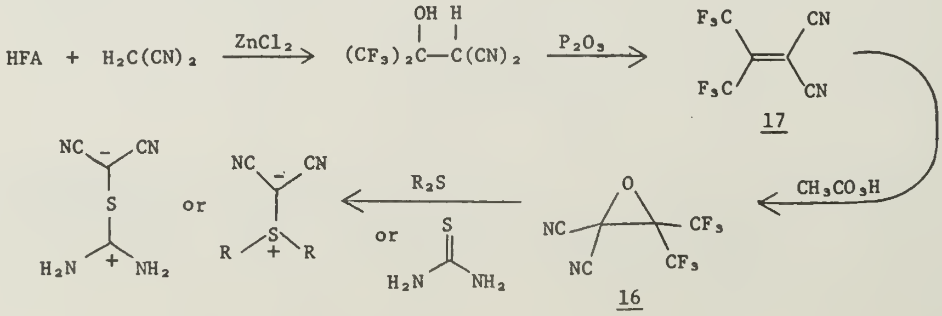
solvent effect for these reactions, and claims to have trapped the zwitterionic intermediate with allyl glycidyl ether.[61] However, other observations are supportive of a more than less concerted mechanism. In the reaction of isobutylene with a twofold excess of HFA only the less thermodynamically stable cis isomer of the 2:1 adduct is isolated and in 97% yield. Examination of the transition state for the concerted addition of HFA to the 1:1 adduct shows that due to the steric demands of the $-CH_2C(CF_3)_2OH$ that the HFA approaches opposite to it, and that the methylene proton leading to the cis isomer is more accessible than the one leading to the trans isomer.[59]

Pattison[62] examined the reaction of propene and 1-butene with HFA under catalytic and non-catalytic reaction conditions. With $AlCl_3$ at -30°C both 2- and 3-alkene-1-ols are formed. However, only 3-alkene-1-ols are obtained in the non-catalyzed reaction. Pattison concluded that in the catalyzed reaction a stepwise mechanism is involved but that the non-catalyzed reaction is concerted.

Finally, the reaction of HFA with β-pinene affords the product one would expect in a concerted reaction; less than 1% of the rearranged product that would be expected if a stepwise mechanism was involved is observed.[61] Thus, it appears that a more than less concerted mechanism is involved in this "ene" type reaction.

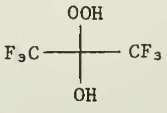


Synthetic Reagents from HFA. Middleton's reagent, 2,2-bis(trifluoromethyl)-3,3-dicyanooxirane, 16, behaves as a source of dicyanomethylene using HFA as the carrier.[63] It is prepared from the condensation of HFA and malononitrile in the presence of $ZnCl_2$ followed by dehydration with



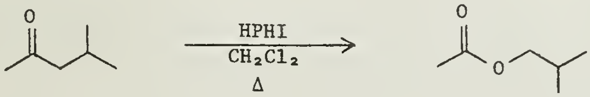
P_2O_5 to 17, 1,1-bis(trifluoromethyl)-2,2-dicyanoethylene. Oxidation of 17 with peracetic acid affords the oxirane. Middleton's reagent reacts with sulfides and thioureas to give the unusually well-stabilized sulfur ylides. Reaction of the sulfur ylides with triphenylphosphine results in the removal of sulfur to give *gem*-dicyano compounds.[64]

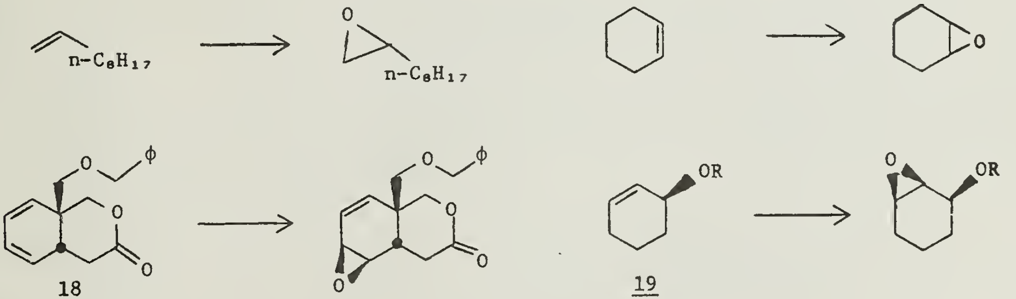
Another reagent, prepared by the reaction of hydrogen peroxide and HFA, 2-hydroperoxyhexafluoro-2-propanol (HPHI), is currently finding wide use as a new selective oxidizing reagent. It was first used in 1970 by Chambers and Clark[65] in the Baeyer-Villiger type oxidation of ketones to esters using mild reaction conditions. Ganem[66] has found that HPHI is also effective in oxidizing alkenes to epoxides. Unlike selenium reagents, HPHI was found to be extremely selective. The reaction of 18 with other oxidizing agents gave all four possible isomers. HPHI gave only the indicated isomer in high yield. HPHI does not react with α,β-unsaturated ketones but does react with allylic ethers, 19, to give stereospecifically *cis* oxidation products. Also found was that the Baeyer-Villiger type oxidation occurs much more slowly than alkene oxidation. In this respect, HPHI is superior to commonly used oxidants such as MCPBA. Recently, Ganem has found that HPHI easily oxidizes aldehydes to carboxylic acids and, unlike chromium and manganese reagents, does not oxidize alcohols.[67,68] Also, HPHI oxidizes amines to amine oxides and sulfides are oxidized with great control to either the sulfoxide or sulfone.[69] What also makes HPHI an attractive oxidant is that its by-product from these oxidations is HFA-hydrate which when treated with hydrogen peroxide regenerates HPHI.



$F_3C-C(OOH)(OH)-CF_3$

(HPHI)





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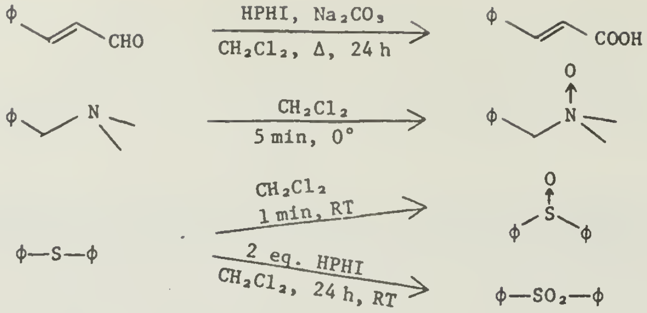

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1980-81, Semester II

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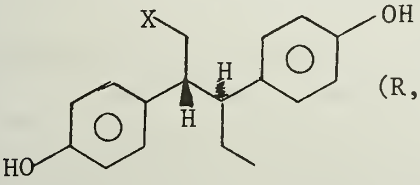
FACTORS INFLUENCING THE BINDING OF NON-STEROIDAL ESTROGENS TO THE ESTROGEN RECEPTOR AND THEIR IMPLICATIONS IN THE DESIGN OF POTENTIAL TUMOR-IMAGING AGENTS

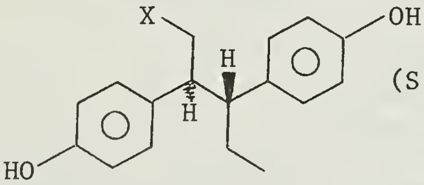
Reported by Scott W. Landvatter January 22, 1981

The biological activity of steroidal hormones, such as estrogens, depends upon an interaction with certain high affinity binding proteins, called receptors. This interaction is characterized by both high affinity and high stereospecificity. This hormone-receptor interaction has been studied through the use of steroidal estrogens (based on estradiol)[1] or through use of non-steroidal estrogens such as hexestrol (meso-3,4-bis(4-hydroxyphenyl) hexane)[2] or norhexestrol (meso-2,3-bis(4-hydroxyphenyl)pentane).[3]

Compared with steroidal estrogens, where substituents are positioned unambiguously within the receptor binding site, hexestrol-based estrogens, owing to a high degree of symmetry and conformational flexibility,[4] can interact with the receptor in four possible binding modes--two per enantiomer.[5]



(R,S)

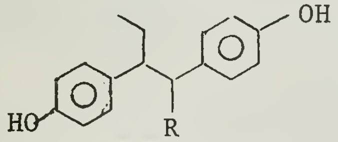


(S,R)

These four modes arise since each enantiomer (R,S and S,R) may place its substituent in the "upper left" of the receptor binding site, or by rotating 180° (i.e., exchanging phenolic positions, which bind simultaneously to receptor), in the "lower right" of the receptor binding site. In order to assess which, if any, of the four modes is preferred, a series of hexestrols and norhexestrols (methyl ester, pentyl ester, alcohol) functionalized on the side chain terminus has recently been prepared.[6]

Binding data to lamb uterine estrogen receptor (Table 1) indicate no appreciable difference in the binding between hexestrol enantiomers. The norhexestrols, on the other hand, do show significant differences in binding,

Table 1. Estrogen Receptor Binding Affinity of Hexestrol and Norhexestrol Derivatives

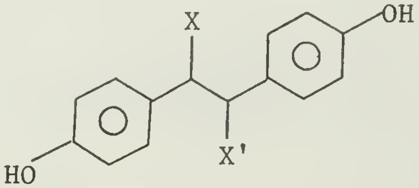


	Receptor Binding Affinity[a] Ratio			
R	racemic	(+)	(-)	(-)/(+)
hexestrol series				
$-CH_2CO_2CH_3$	20.0	19.1	20.5	1.07
$-CH_2CO_2$n$-C_5H_{11}$	4.2	4.5	4.7	1.04
$-CH_2CH_2OH$	16.2	17.8	15.5	.87
norhexestrol series				
$-CO_2CH_3$	69.2	37.2	77.7	2.09
$-CO_2$nC_5H_{11}	38.9	5.3	77.7	14.66
$-CH_2OH$	8.9	6.3	10.2	1.62

[a] Affinities are measured relative to estradiol (=100).

with the (-) pentyl ester binding nearly 15 times as well as its (+) antipode. Similar, though less dramatic differences are observed with the normethyl ester and alcohol. These comparisons suggest that a source of the chiral recognition is a specific interaction between the carbonyl group in the (-)-2R,3S enantiomer[3,7] of the norhexestrol derivative that elevates affinity (perhaps by accepting a hydrogen bond), this interaction not being attainable in the other enantiomer or in the derivatives in the hexestrol series.

The question of binding mode is less well defined. Hexestrols with two bulky substituents bind poorly to receptor,[8] indicating that either the upper left region of the receptor or the lower right should be able to tolerate a bulky substituent, not both. Since hexestrols show no differences in binding between enantiomers, they can adopt two of the four modes equally. The norhexestrols, on the other hand, do display non-equivalent binding between enantiomers. Therefore, the norhexestrols must prefer only one of the four binding modes. Unfortunately, it is not possible to ascertain which region of the receptor can actually tolerate the bulky substituent.



X=X'=n-butyl

X=X'=i-butyl

Several other side chain-functionalized hexestrols and norhexestrols have been synthesized and have had their receptor binding affinity measured (Table 2).[9] These binding results can be nicely rationalized by a receptor binding model sensitive to three factors: size of the substituent, lipophilicity of the substituent, and the ability of the substituent to engage in the previously described hydrogen-bonding interaction.

Table 2. Binding Affinities of Hexestrols and Norhexestrols to the Estrogen Receptor

	Relative Binding Affinity	
Compound	Norhexestrols	Hexestrols
1° amide	0.18	0.06
pentyl amide	0.32	0.13
1-diazo-2-keto	10.5	2.8[a]
methyl ketone	31.6	20.4
butyl ketone	93	9.1
fluoro	132	129[b]
bromo	186	71[b]
iodo	172	60[b]
alkane	129	300

[a] Data is from J. Park and J. A. Katzenellenbogen, unpublished.

[b] Data is from reference 2.

The 1-halonorhexestrols, for example, are particularly sensitive to steric effects. Here binding affinity decreases with increasing size: F>Br>I. The fluorohexestrol is approximately isosteric with hexestrol (RBA=300), but due to its increased polarity binds less well than hexestrol itself. The bromo and iodo derivatives are better in terms of polarity, but their large size precludes high binding. In the 1-halonorhexestrols, the situation is somewhat different. Now the bromo and iodo derivatives are isosteric with hexestrol. Since these substituents also have low polarity, they show very high binding to receptor. The fluoronorhexestrol is now too small and too polar, thus this compound shows an affinity less than the other halonorhexestrols.

These halogenated derivatives are currently being investigated as potential tumor-imaging agents.[10] Some 60% of primary human breast tumors contain detectable levels of estrogen receptor,[11] and in many cases this level is greater than in normal breast tissue. Thus, selective localization of an estrogen labeled with a radiohalogen, such as ^{18}F, ^{77}Br, ^{123}I or ^{131}I should allow detection of receptor containing primary breast tumors and perhaps metastatic tumors as well.

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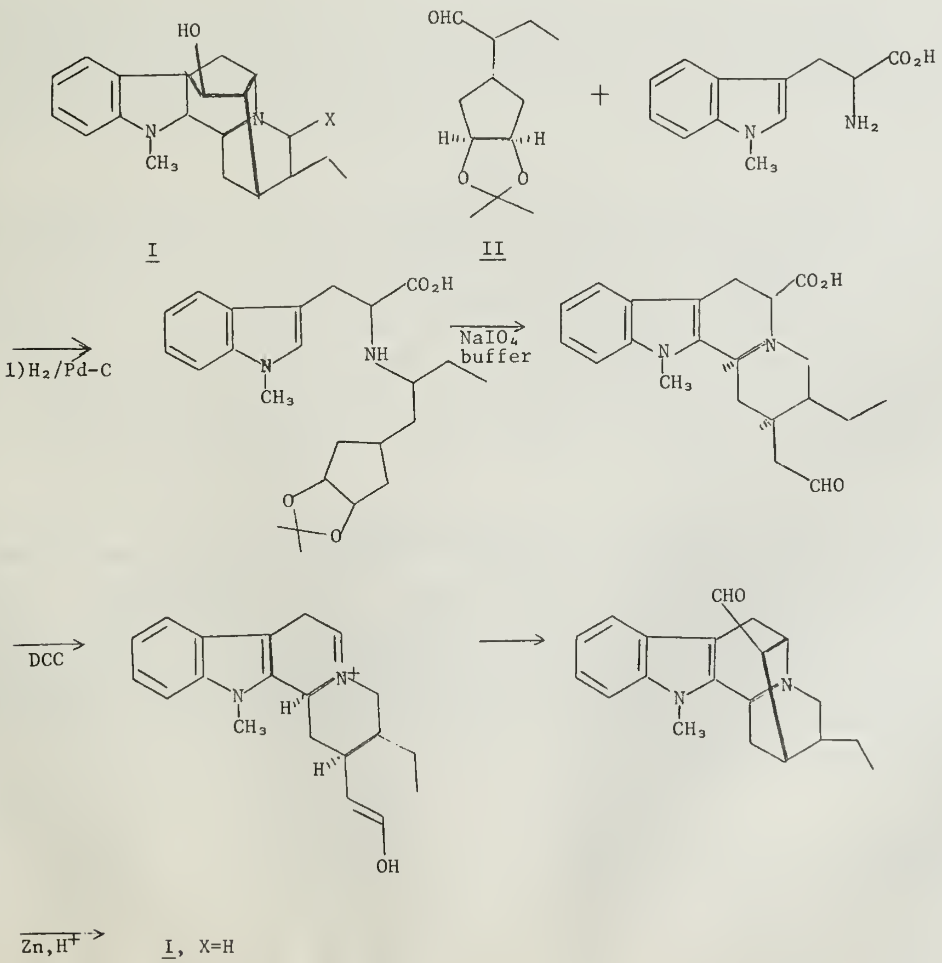
BIOGENETIC-TYPE SYNTHESES OF SOME ISOQUINOLINE AND INDOLE ALKALOIDS, OR "THE NATURAL WAY TO SYNTHESIZE"

Reported by David Kinder January 26, 1981

Biogenetic-type syntheses are patterned after presumed or verified biogenetic pathways. Starting materials are designed to maintain the reaction type of key steps of the biogenetic pathway, but modifications of the reagents may range from trivial to extensive.[1] A synthesis patterned in this fashion is usually economical in terms of steps used and yields obtained and support for a proposed biogenetic intermediate (i.e., one not isolated from in vivo experiments) can be gained. Van Tamelen[1] discusses the merits and types of biogenetically styled syntheses in early reviews. Because of their diverse biological properties (e.g., analgesics, antineoplastic agents), indole and isoquinoline alkaloids have received much attention, both from synthetic as well as biosynthetic standpoints. While the topic has been reviewed,[3] this seminar covers more recent work. Biochemical pathways will not be presented here, but can be found in recent reviews.[2]

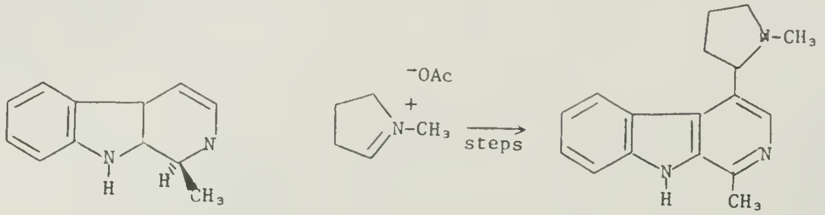
Many indole alkaloids are derived from tryptamine (or tryptophan) and secologanin. The heteroyohimbines and biogenetic precursors of the Coryanthe series have been synthesized via biogenetic-type synthesis.[4] The synthesis of ajmaline[5] (I, X=OH) shown in Figure 1 illustrates use of a biochemical analog (II) of secologanin. The synthesis of adirubicene is similar.[6]

Figure 1



The above synthesis can be compared to a synthesis of brevicolline (III) in which substrates are more natural.[7] Key steps are indicated in Figure 2 where N-methyl-Δ'-pyrrolinium acetate (IV) derived from ornithine and dihydro-β-carboline (V) are condensed.

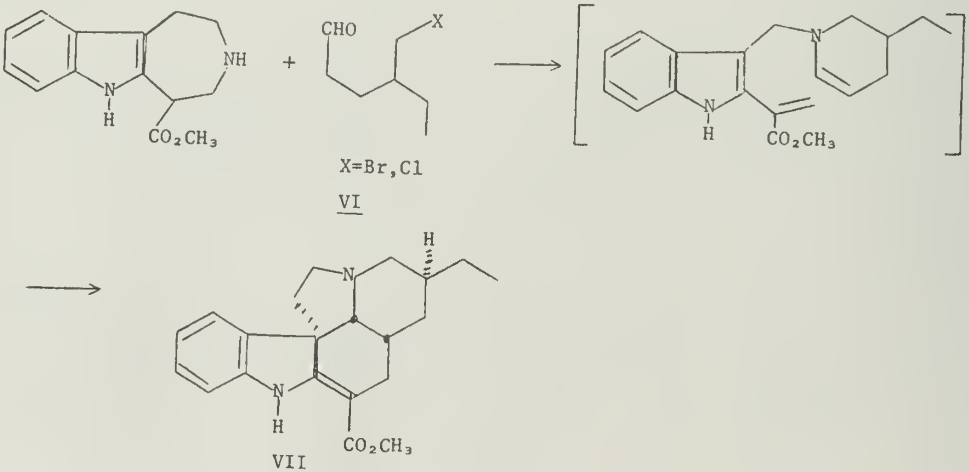
Figure 2



V IV III

Vincadifformine and related alkaloids[8,9] are biogenetically related to adirubicene. The skeletal rearrangement involved is postulated to proceed through a fragmentation which sets up a Diels-Alder reaction. Based on this assumption, Kuehne et al.[8] have synthesized vincadifformine, Ψ-vincadifformine, and the dehydro analogs tabernine and Ψ-tabernine. The key steps in formation of Ψ-vincadifformine (VII) are shown in Figure 3. A portion of secologanin is represented by aldehyde VI.

Figure 3

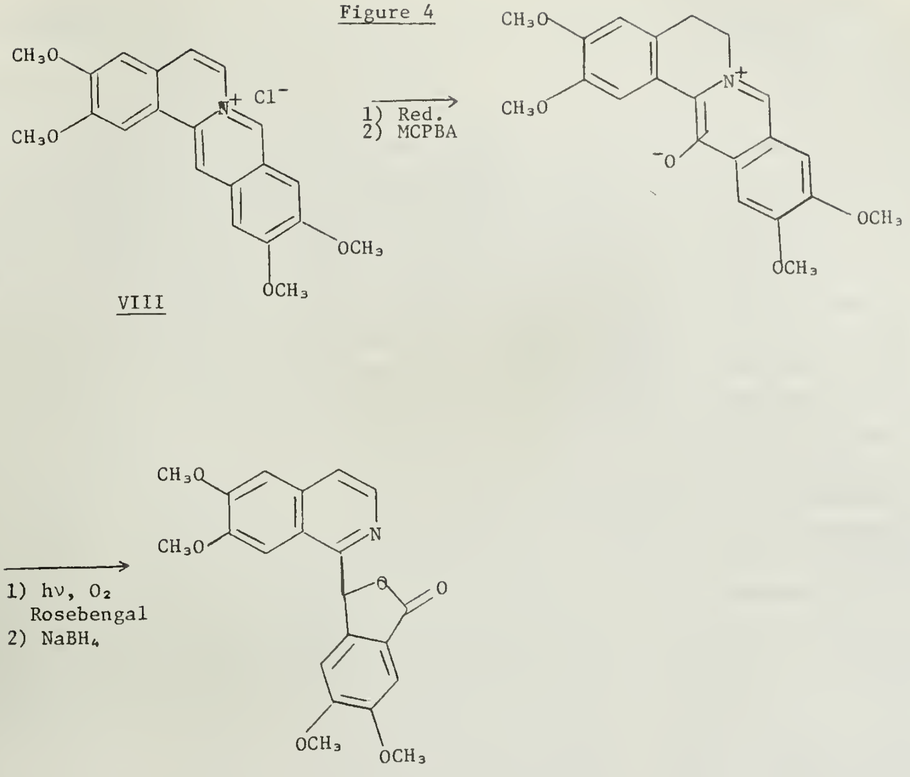


VI

VII

Isoquinoline alkaloids have also been synthesized in biogenetic-type reactions. The berberine[10] alkaloids are derived from benzylisoquinolines, and the phthalideisoquinoline alkaloids[10e] from berberines. Conversion of berberines to phthalideisoquinolines involves oxidation followed by rearrangement. This has been accomplished photochemically,[10a-c] with metal oxides,[10d,f] as well as N-oxides.[11] Figure 4 shows the photochemical conversion of the 8-norcoralyne salt (VIII) into phthalideisoquinoline IX.[10a] IX has been converted to hydrastin analogs.[9d]

Figure 4



VIII

IX

The *Amaryllidaceae* alkaloids[12] are interesting because they involve oxidative phenolic coupling of tyrosine after condensation with an appropriate aldehyde. Space prohibits adequate discussion of these alkaloids; the interested reader is directed to the cited articles.

Nature usually is highly efficient in designing a synthesis. If we as chemists emulate nature in our planning of a synthesis, we too should be able to develop efficient routes to complex molecules. In some instances, a biogenetic-type synthesis provides the only reasonable route to a complex structure. It is tempting to draw conclusions about natural processes from a synthesis patterned after a biogenetic scheme. While no synthesis confirms a biogenetic pathway, insights may be gained about the actual enzymatic reactions. These insights can lead to more effective testing of a biogenetic pathway, eventually solving a complex biochemical riddle.

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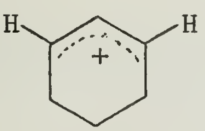
DEUTERIUM ISOTOPE EFFECT ON CARBON-13 NMR: ITS APPLICATION TO THE "NONCLASSICAL CARBONIUM IONS" PROBLEM

Reported by A. Bashir-Hashemi January 29, 1981

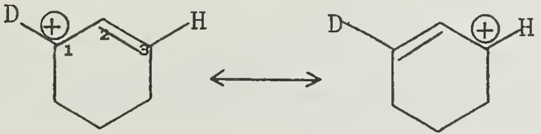
Among the most impressive accomplishments in organic chemistry during the last decade has been the development of a variety of experimental tactics for the direct observation of reactive carbocation intermediates in solution.[1] The pioneering and systematic efforts of Olah, Saunders, Brouwer and Hogeveen have resulted in a multitude of NMR, vibrational IR, and Raman and ESCA spectroscopic data on literally hundreds of carbon-containing ions in super acid media where these ions are stable and long-lived.[2] Despite this burst of activity, the detailed geometrical structure of not a single such ion is yet known.[3] Recently, information has been obtained about the structure of carbocations by using deuterium isotope effects on carbon-13 NMR spectra.[4]

Kinetic deuterium isotope effects are widely used for studying reactions, particularly those involving carbonium ions.[5] Isotope effects measured in solvolysis kinetics are related to energy differences between starting materials and transition states and give no direct information about the cations. M. Saunders and his coworkers have reported a new and accurate method for the measurement by NMR of equilibrium deuterium isotope effects in cations and other systems undergoing rapid degenerate rearrangements.[4]

It has been found that the ^{13}C NMR spectra of 1-deuterium cyclohexenyl cation (1), displays small isotopically induced splittings of the downfield carbon (C_1 and C_3) resonance due to a novel kind of isotope effect.[6] These observations suggest a way to qualitatively distinguish between systems which are delocalized and symmetrical and systems which are instantaneously asymmetric, but symmetrical on the NMR time scale because of rapid degenerate rearrangement. The splitting between C_1 and C_3 represents a novel isotope effect which has been called isotopic perturbation of resonance. This is related to the common substituent effects on resonance. One might consider this new isotope effect in a similar way, concluding that deuterium substitution increases the effective importance of one canonical form over the other. Since the proton substituted carbon is shifted downfield, and the deuterium substituted carbon upfield, ion Ib contributes more to the "average" species than does ion Ia, i.e., the positive charge prefers to be on the carbon bearing the proton.



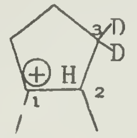
I



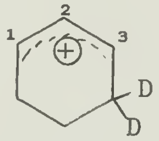
Ia Ib

One can compare experimental phenomena of isotopic perturbation of resonance with analogous equilibrium isotope effects.[8] In both cases, in the isotopic compound, pairs of ordinarily equivalent nuclei give doublets split approximately symmetrically about their ordinary chemical shift. The difference is that, in the equilibrium case, we have an energy surface with two minima separated by a low barrier and observe the isotopic influence on their relative stability. In the resonance case, there is only one minimum and we observe the change in the single structure, averaged over vibration, upon isotopic substitution.

The splitting in the ^{13}C NMR is considerably smaller for isotopic perturbation of resonance than for equilibrium isotope effects. The relative splitting, δ/Δ (where δ is the isotope splitting and Δ the chemical shift difference estimated for the "frozen" equilibrium), is an indicator of the extent of delocalization. Large values of δ/Δ indicate isotopic perturbation of equilibrium, while small values are characteristic of isotopic perturbation of resonance.[6,7,8] Thus in the ^{13}C NMR spectrum of the dimethyl cyclopentyl ion II, the peaks for C_1 and C_2, which are averaged in the undeuterated



II

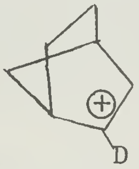


III

ion, are split by 105 ppm at -130°C[7] whereas for the cyclohexenyl cations I[6] and III,[9] peaks for C_1 and C_3 are split by 0.33 and 0.83 ppm. The δ/Δ values of 0.2, 0.0038 and 0.008 are obtained for II, I and III respectively.[9]

"The nonclassical carbonium problem," is at the center of the carbocation's investigations.[3,8,10,11] Both the explanation of the solvolysis kinetics and the structure of the stable "nonclassical carbonium ions," such as norbornyl cation (IV)[2] have long been at issue. The argument over the stable cations concerns whether it is a rapidly equilibrating pair of classical ions or rather a symmetric (nonclassical) species.[10]

Saunders and his coworkers have recently reported application of the deuterium isotope effect on ^{13}C NMR to the problem of the structures of the nonclassical carbonium ions.[6,7,8,12,13] For the norbornyl cation IV the



IV

value of 0.008 is obtained for δ/Δ.[13] The postulated rapid Wagner-Meerwein rearrangement in the norbornyl cation is not consistent with this result, but a static, symmetrical structure is.

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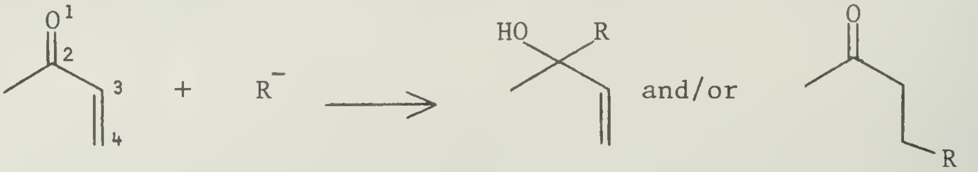
FACTORS CONTROLLING THE REGIOSELECTIVITY OF ADDITIONS TO α-ENONES UNDER KINETIC OR THERMODYNAMIC CONTROL

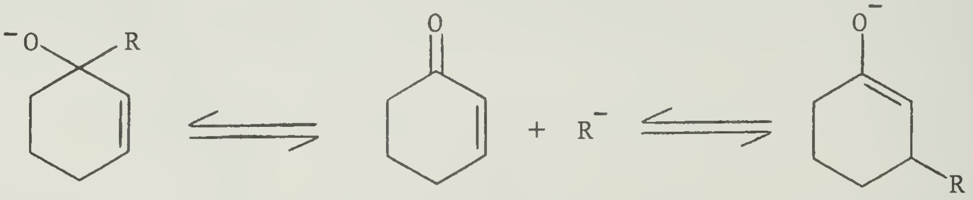
Reported by Larry Last February 2, 1981

Reactions of carbanions with α,β-unsaturated carbonyl systems have long been known to afford products derived from 1,2-(direct) and/or 1,4-(conjugate) addition[1] (Eq. 1). More recently, experiments have been aimed at demonstrating the reversibility of such reactions in terms of kinetic versus thermodynamic control.[2-9] Experimental parameters, such as reaction time and temperature,[4,5,7,8,10-13] solvent,[6,9,14,15] added complexing agents,[14,16-22] substituents,[3,12,23-25] and counter ions[26,27] have all been shown to play a role in determining the ratio of direct and conjugate addition products.



(1)

In 1976, Schultz and Yee[5] suggested that an equilibrium might be established between direct and conjugate addition products upon the addition of ester enolates to α-enones (Eq. 2). They further felt that if kinetic addition occurs at the carbonyl carbon and equilibration leads to conjugate addition, then selective product formation should be possible by careful control of reaction time and temperature. This was found to be the case, as 1,2-addition products predominate under kinetic conditions (low temperature and short reaction times), whereas 1,4-addition products are favored under thermodynamic conditions (high temperature and long reaction times).[28] Subsequent studies have substantiated this trend.[7,8]



(2)

Solvent "donicity" also affects the regioselectivity of addition, with direct addition products being favored in solvents with a low donor number and conjugate addition products in solvents with a high donor number.[6,29,30] Addition of an agent capable of complexing the cation, such as HMPA,[14] crown ethers,[26] or cryptands[29] also results in a preference for conjugate addition. This is in accord with the theoretical prediction that Li^+ complexation by the C=O of the enone favors 1,2-addition, whereas in strongly Li^+ solvating media where complexation is less likely, more 1,4-addition is expected.[8,27]

Substituents on both the carbanion and the enone can direct the addition. In fact, Mulzer and coworkers[24] have achieved a continuous transition from 1,2- to 1,4-addition under kinetic control by means of varying the steric requirements and resonance capabilities of the substituents. The effect of varying the cation has also been considered.[26,27]

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SLOW REACTING SUBSTANCES OF ANAPHYLAXIS: THE LEUCOTRIENES

Reported by Srinivasan Nagarajan February 5, 1981

Arachidonic acid is a biosynthetic precursor to several biologically important compounds (e.g., prostaglandins, thromboxanes, prostacyclins).[1] The latest addition to this impressive list is a group of compounds collectively known as slow reacting substances of anaphylaxis. These compounds are so called because they induce a slow and prolonged contractile response in smooth muscles such as lungs.[2] These compounds are produced in response to immunological challenge[3] and to addition of certain stimuli[4] to smooth cell preparations. SRS are primary mediators in asthma and immediate-type hypersensitivity.[5] Their role in respiratory system diseases and the problems chemists faced in terms of their structural elucidation evoked recent interest. In the past two years, the structures of several SRS's have been elucidated in detail and confirmed by unambiguous syntheses. These structure elucidation and the syntheses will be the major concern of this review.

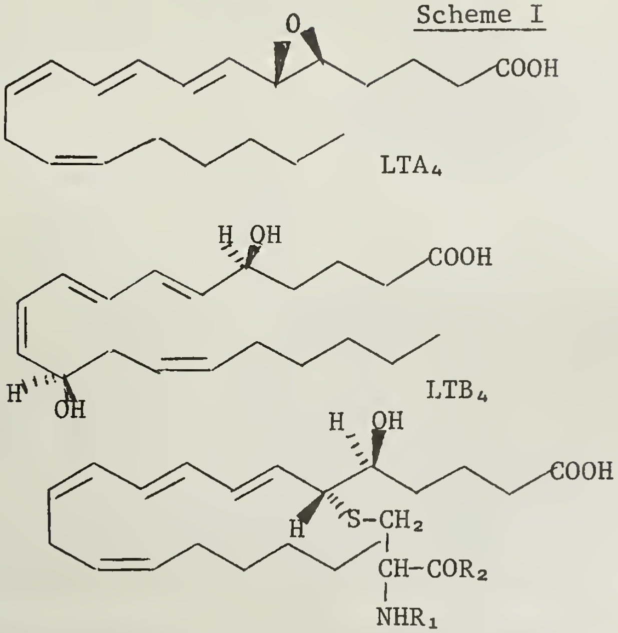
In 1938 Feldberg and Kellaway[2] introduced the term slow reacting substances to describe a smooth muscle contracting activity which appeared in the effluent of profused lungs of guinea pigs which were treated with cobra venom. Kellaway and Trethewie[3] later showed that a similar activity could be produced by the action of specific antigen on sensitized guinea pig lungs in vitro. Also this activity was proved not to be due to histamine since an added amount of antihistamine in the preparation did not inhibit contraction.[6] During the next several years, the formation and release of SRS from tissues and isolated cells were studied in great detail. SRS is formed and released from rats, guinea pigs and human lungs during immunologica challenge.[7] SRS is also released in response to non-immunological stimuli, e.g., calcium ionophore A23187.[8] It has been recently demonstrated that large quantities (micrograms) of SRS can be released from rat peritoneal mononuclear cells,[9] rat basophilic leukemic cells,[10] murine mastocytoma cells[1 and from human leukemic basophils[12] by appropriate challenge. Despite a plethora of sources, similar activity was observed in all cases.

When lung tissues of two asthmatic patients were exposed to pollens (birch trees and timothy grass) to which the patient (from whom the lung was removed) was allergic SRS-A was produced in vitro. The presence of an antihistamine did not prevent bronchile preparations from these patients from releasing SRS-A upon exposure to specific allergens.[13] When normal guinea pigs were given an intravenous injection of SRS-A (40-120 units) a marked increase in the resistance of the lungs to inflation was observed.[14]

Chemical identification of SRS-A was elusive for several reasons. The normal concentration of SRS-A in cells is of the order of few picograms. The SRS's from cell preparations were not pure and were mixtures of several components. The disappearingly small quantities of these unstable substances resisted conventional purification techniques. Using HPLC and radiolabelling techniques these problems were circumvented.

Nomenclature.[15] This new group of compounds was originally discovered in leukocytes[16] and they all have the characteristic UV recognizable triene chromophore. Hence the name leukotrienes. The different members of the group are identified by A, B, C and D, etc. Additionally a subscript designates the total number of double bonds in the molecule. Examples of this nomenclature are given in Scheme I.

Scheme I



	R_1	R_2
LTC₄	γ-glu	gly
LTD₄	H	gly
LTE₄	H	OH

LTC₄. The possibility that arachidonic acid and cysteine could be precursors for SRS was confirmed by the incorporation of radiolabelled arachidonic acid[17] and the increased production of SRS by the addition of cysteine to the incubation medium.[18] High specific radiolabelled compounds were used to explore the structure of LTC₄.[19] Radiolabelled compounds in general, were added, 15 minutes to 1 hour before the addition of ionophore to the medium. Since the SRS-A's have characteristic UV maxima at 280nm this was used as a guide in purification and isolation. In the case of LTC₄, murine mast cells were used with calcium ionophore A23187. HPLC was used to separate the various components. LTC₄ was the major product in the case of murine mast cells. The incorporation data is given in the table.

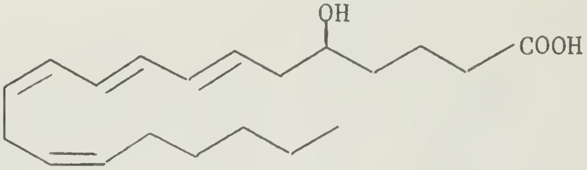
Table 1

Exp. 1		Exp. 2		Exp. 3	
$[^3H]C_{20:4}$	^{35}S cys	3-^3H cys	^{35}S cys	3-^3H cys	U-^{14}C cys
0.027%	0.056%	0.014%	0.02%	0.002%	0.0022%

The incorporation data obtained with ^{35}S, 3-^3H, U-^{14}C cysteine indicated that all the carbon atoms, sulphur and C-3 hydrogen are present in LTC₄. With [5,6,8,9,11,12,14,15-$^3H_8$] arachidonic acid, it was concluded that all the carbon atoms of arachidonic acid are also present in LTC₄.

When a sample of LTC₄ was subjected to oxidative ozonolysis and the products analyzed by glc/ms the presence of Glutaric acid was revealed. When ^3H labelled LTC₄ was subjected to reductive ozonolysis (with $NaBH_4$) radioactive 1-hexanol was obtained. Desulfurization of LTC₄ was effected with Raney Nickel. The mass spectrum of the product was identical to that of 5-hydroxy arachidic acid. The mass spectrum of the TMS derivative indicated the presence of one, two and three double bonds (due to partial hydrogenation). When LTC₄ was treated with lipoxygenase (an enzyme which requires the presence of 1,4 cis diene) it showed a bathochromic shift of 30 nm.

The UV spectrum of lipoxygenase treated product may be attributed to a conjugated tetraene and that of LTC_4 to a conjugated triene. When these pieces of information are put together one concluded that structure 1 represents that of desulfurized LTC_4.



1

Treatment of LTC_4 with Raney Nickel indicated that the amino acid residue was attached through the sulfur linkage. Attachment of the amino acid portion to C_1-C_5 and C_{15}-C_{20} is excluded since glutaric acid and 1-hexanol are obtained upon ozonolysis. Substitution on the triene chromophore is excluded on the basis of the observed UV absorption. This leaves positions C-6, C-14 and C-13. Positions C-13 and C-14 can be ruled out because LTC_4 reacts with soyabean lipoxygenase. Hence LTC_4 is 5-hydroxy-7,9,11,14-eicosatetraenoic acid with the amino acid portion attached at C-6 through the sulfur. At this stage the geometry of the C-7 and C-9 double bonds was assumed to be trans and later confirmed by synthesis.

Raney Nickel treatment of LTC_4 did not give any alanine, implying that cysteine is further derivatized.[19] The amino acid analysis indicated the presence of glutamic acid, glycine and cysteine per equivalent of LTC_4.[20] End group analysis by the dansyl method and by hydrazinolysis showed amino terminal glycine and carboxy terminal glutamic acid. Failure of the dansyl Edman degradation to give glycine after two cycles indicated that the glutamic acid is present as a γ-glutamyl derivative. Thus the amino acid part was concluded to be glutathione, a naturally occurring tripeptide.

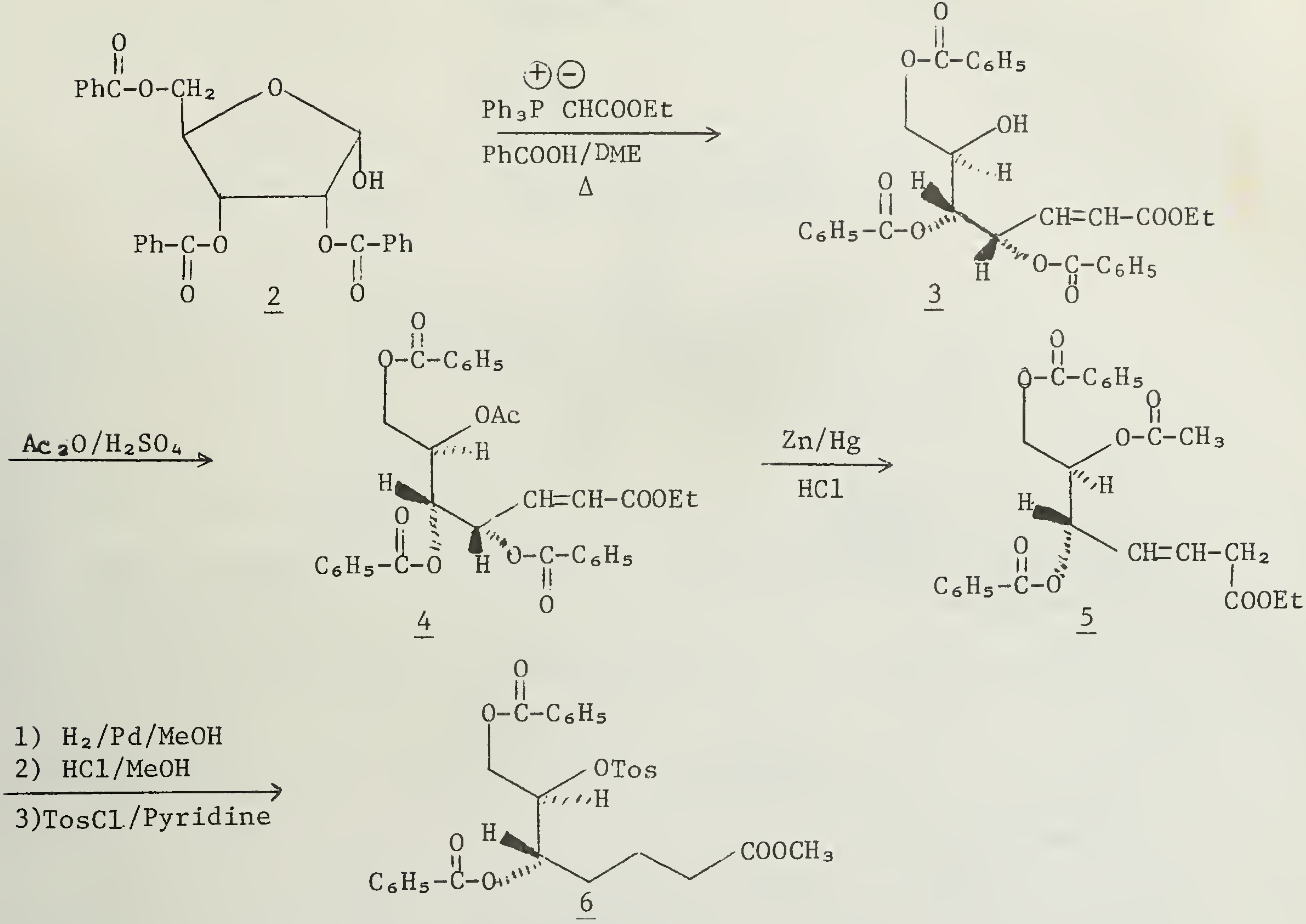
Three syntheses of LTC_4 are known to date. Corey's[21] synthesis was designed to settle the question of stereochemistry by using starting materials with known absolute stereochemistry. The unambiguous nature of the synthesis and the comparison of the synthetic product with natural LTC_4 provided the rigorous proof of the structure. The starting compound for this synthesis is the readily available 2,3,5-tribenzoyl derivative of D(-) ribose, the configuration of which is known. This was converted in high yield to stable intermediate 6 in five steps as shown in Scheme II.

On treatment with five equivalent of potassium carbonate, tosylate 6 gave trans epoxide 7. Oxidation of 7 with Collins reagent gave aldehyde 8. From 8 the synthesis was carried to trans-5(S), 6(S)-oxido-7,9-trans 11,14-cis eicosatetraenoic acid methyl ester 10 as shown in Scheme III.

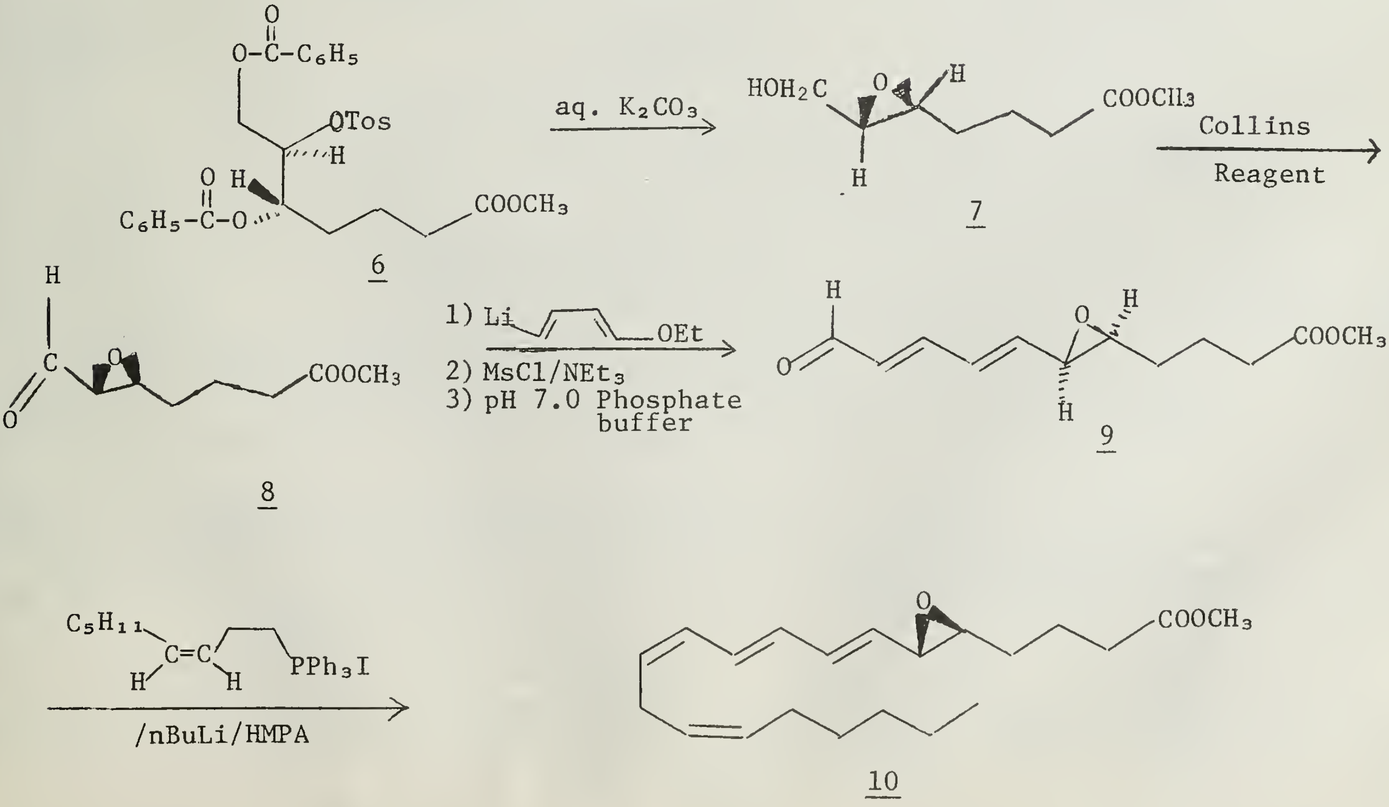
A single coupling product was obtained from the reaction of 10 with N-trifluoroacetylglutathione dimethyl ester and triethylamine in methanol (SN_2 conditions). Selective hydrolysis of the trifluoroacetyl and dimethyl ester groups gave pure LTC_4 as proved by HPLC. The synthetic material was indistinguishable from natural LTC_4.

The synthesis of LTC_4 by Rokach et. al.[22] was designed even before the identity of the amino acid part was established. What they thought to be a synthesis of a leukotriene with SRS-like activity actually turned out to be a synthesis of LTC_4. Even though their approach was few steps shorter than

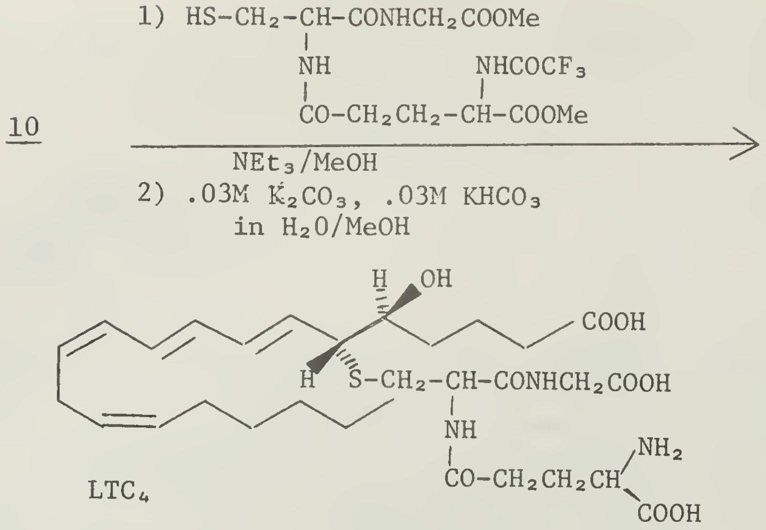
Scheme II



Scheme III

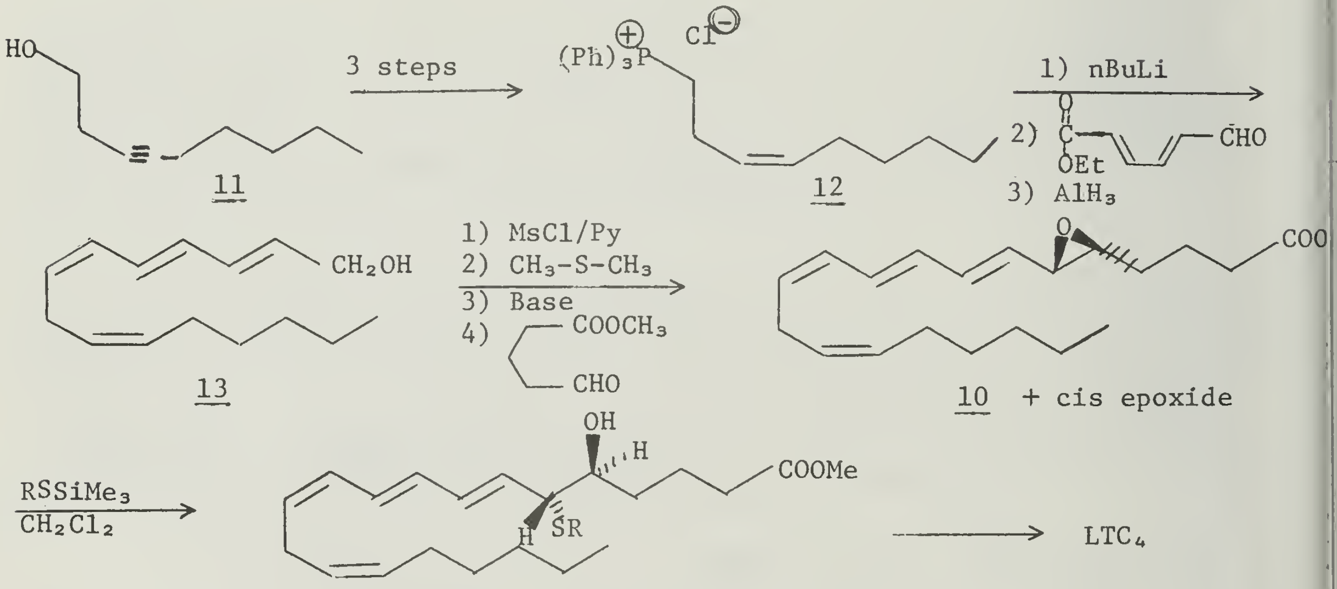


Scheme IV



Corey's, it involved separation of isomers at two different stages. This synthetic approach is summarized in Scheme V.

Scheme V



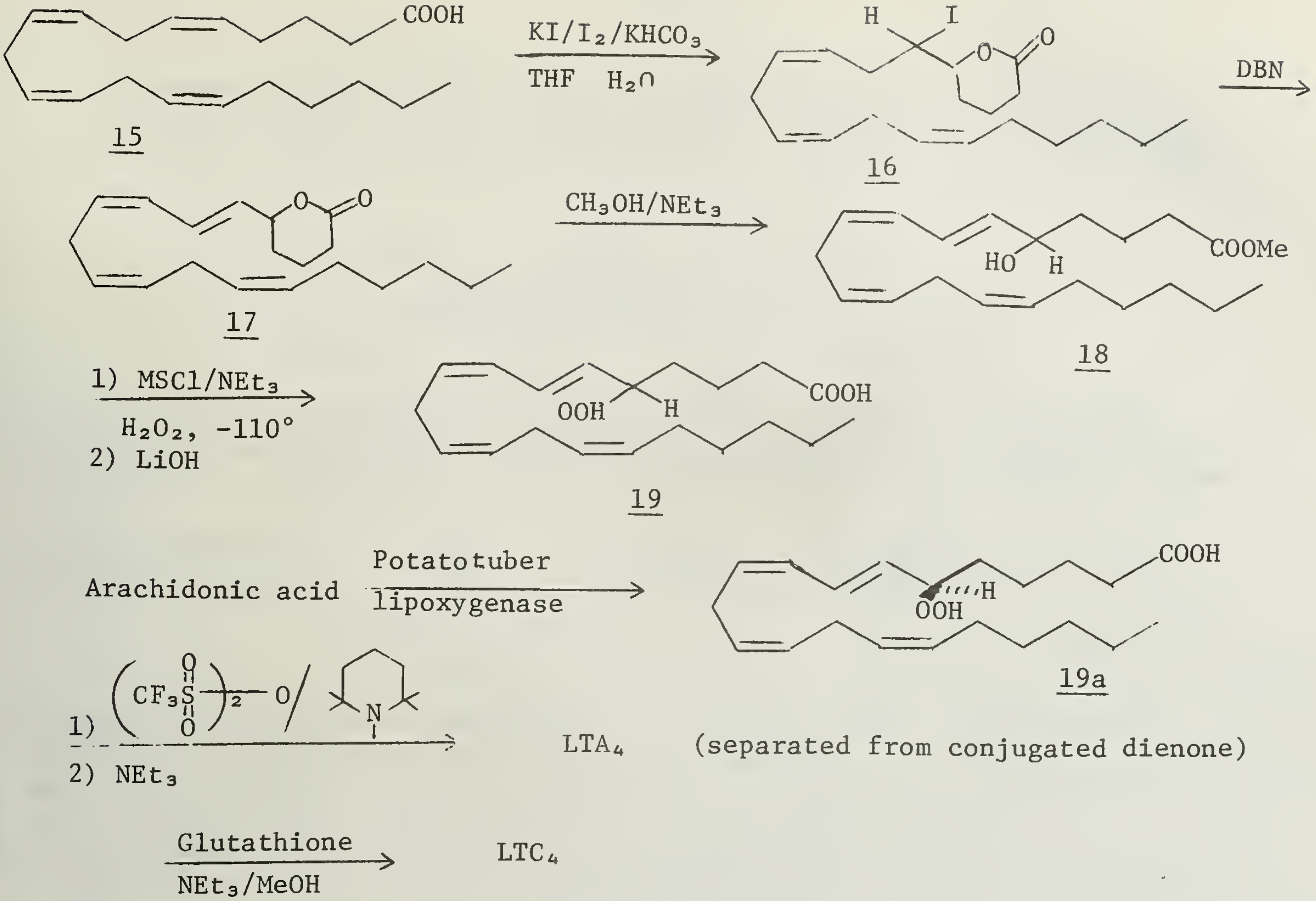
14 + other diastereomer

R: Blocked glutathione

A biomimetic type synthesis was also done by Corey et. al.[23] starting from arachidonic acid, the proposed biosynthetic precursor (vide supra). Though the number of steps were few, the yields were not good. Leukotriene A was obtained from arachidonic acid both by chemical and enzymic synthesis (Scheme

LTD₄. On treatment with calcium ionophore A23187 rat basophilic leukemia cells release a slow reacting substance.[24] RBL SRS has a UV maximum at 280 nm but elutes prior to LTC₄ in silicic acid chromatography. Desulfurization gives 5-hydroxyarachidic acid indicating that the fatty acid part of RBL SRS is same as that of LTC₄. Treatment of RBL SRS with lipoxygenase gives similar results. Amino acid analysis shows equivalent amounts of glycine and cysteine but no glutamic acid. When LTC₄ is treated with γ-glutamyl transpeptidase RBL SRS is obtained. The structure of RBL SRS

Scheme VI



15

16

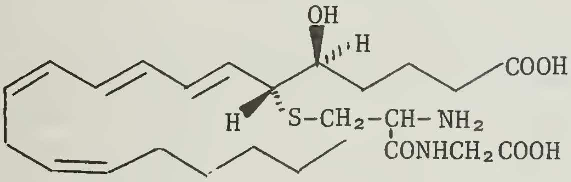
17

18

19

19a

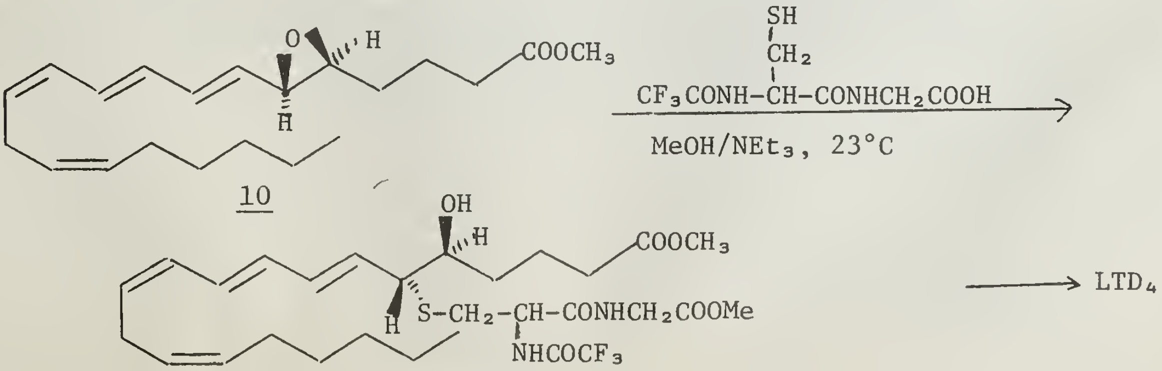
is therefore 5-hydroxy-6-(S)-cysteinylglycyl-7,9,11,14-eicosatetraenoic acid. RBL SRS was later named LTD₄.



LTD₄

The LTD₄ can also be obtained from rat mononuclear cells by treatment with calcium ionophore A23187.[25] LTD₄ has been found to be the most potent of all the leukotrienes. It accounts for 90% of the biological activity in hypersensitized human lungs.[26] LTD₄ was synthesized in a similar manner to that of LTC₄ from LTA₄.[27] N-Trifluoroacetylcysteinylglycine methyl ester was allowed to react with LTA₄ methylester in the presence of triethylamine in methanol at 23° under argon to afford the N-trifluoroacetyl dimethylester of LTD₄. Deprotection gave LTD₄ in 90% yield. The natural and synthetic LTD₄ were indistinguishable by HPLC and bioactivity.

Scheme VII



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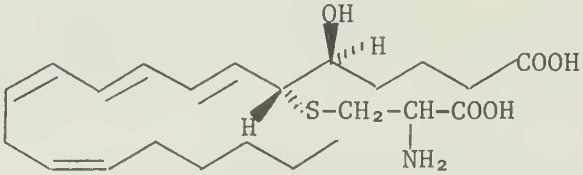
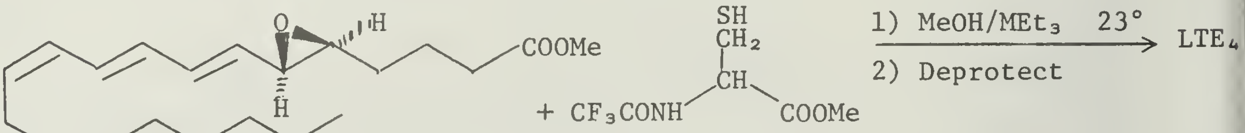
LTE$_4$. The rat peritoneal cavity produced a SRS on Ig Ga dependent anaphylaxis.[28] Three active peaks separated on HPLC. Two of them were identified as LTC$_4$ and LTD$_4$. The third peak was identified as LTE$_4$ by comparison with synthetic LTE$_4$.



LTE$_4$

Reaction of N-trifluoroacetyl L-cysteine methylester with LTA$_4$ methylester in methanolic triethylamine at 23° afforded N-trifluoroacetylleukotriene E$_4$ dimethylester. Deprotection gave LTE$_4$ in good yields.



10

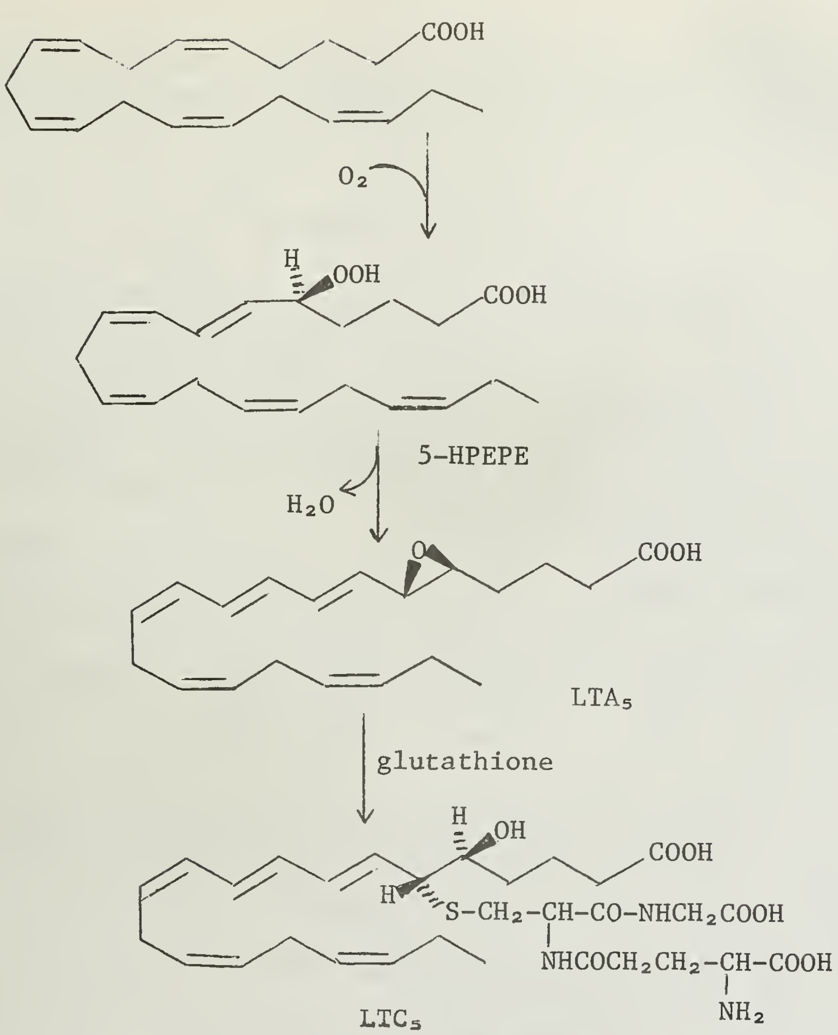
20

LTA$_4$ and LTB$_4$. LTA$_4$ is probably a biosynthetic precursor to all SRS-A's and is quite unstable.[29] LTC$_4$, LTD$_4$ and LTE$_4$ were all synthesized from LTA$_4$ by using appropriate peptide or amino acid.[30] Several syntheses of LTA$_4$ are known to date[31] (vide infra). LTA$_4$ has no SRS activity. On treatment with acid, LTA$_4$ gives LTB$_4$[32] which also has no SRS activity. When arachidonic acid is metabolized in polymorphonuclear leukocytes, LTB$_4$ is formed among other products.[33]

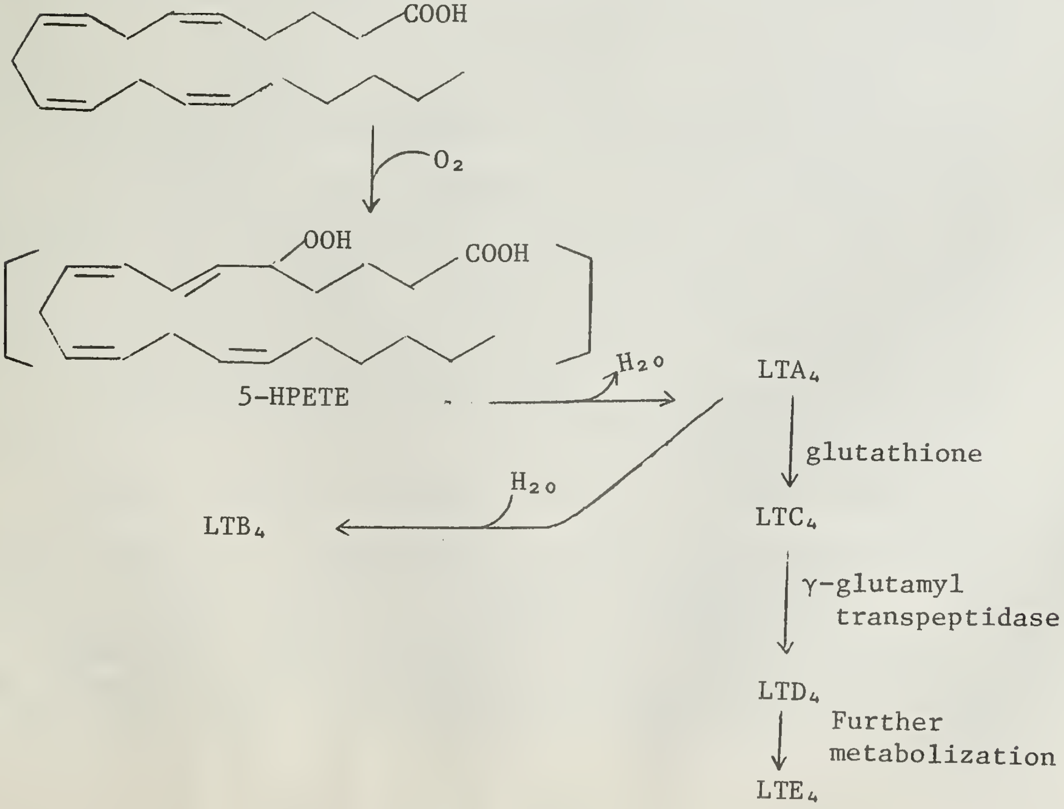
LTC$_5$. When 5,8,11,14,17-eicosapentaenoic acid is incubated with mouse mastocytoma cells and calcium ionophore A23187, two products are obtained.[34] One is LTC$_4$. The other earlier eluting product has been identified as LTC$_5$. The UV spectrum of LTC$_5$ is indistinguishable from LTC$_4$ and the same spectral change is observed upon incubation with lipoxygenase. This leads to the conclusion that the triene chromophore is intact in LTC$_5$. Amino acid analysis indicated the presence of the glutathione moiety. It was concluded that LTC$_5$ has one more double bond than LTC$_4$, the position and geometry of the double bond is assumed to be the same as that of eicosapentaenoic acid (i.e., 17 cis). The formation of LTC$_5$ can be picturized as in Scheme VIII.

Structure-activity Relationships. The amino acid part at C-6 is essential for activity and the amino acid and carboxyl groups must be free. Acetylation and/or esterification destroys the activity.[35] The positional isomer of the S-peptide in LTC$_4$ (at C-12) is not active.[36] When the peptide is cys-gly, the SRS is most active.[37] Addition of γ-glu (LTC$_4$) or removal of gly (LTE$_4$) from this peptide reduced the activity.[37] The geometry of the C-11 double bond must be cis. When it is trans, the activity is markedly reduced.[38] The -CH$_2$- at C-13 also seems to be essential for SRS activity, for, when SRS is treated with lipoxygenase, the -CH$_2$- is used up and the activity is lost.[39] Epimerization of LTC$_4$ at C-6 and C-5[40] or an extra double bond at C-17[41] reduced the activity of SRS.

Scheme VIII



Scheme IX. Proposed biosynthetic pathway



The discovery of new compounds is always exciting. With the structures and syntheses of these active compounds known, the pathology of these compounds could be studied extensively which was not possible until now. This would hopefully lead to the design of drugs for treating asthma and other similar diseases.

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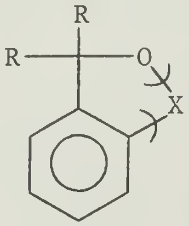
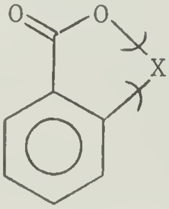
A TRIDENTATE LIGAND USEFUL IN STABILIZING HIGHER COORDINATION STATES OF NON-METALLIC ELEMENTS. AN ARYLDIALKOXYBROMINANE (10-Br-3) AND AN ARYLDIFLUORODIALKOXYPERIODINANE (12-I-5)

Reported by Tuyen T. Nguyen February 9, 1981

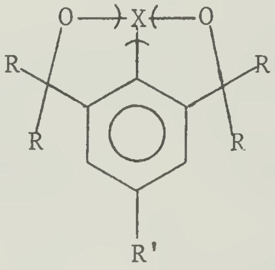
Hypervalent bonding[1] is known to be favored by electronegative ligands[2] as observed in many examples of hypervalent compounds of non-metals.[3] Various bidentate and tridentate ligands, such as 1a, b, 2, 3a, and 4 have been shown to be useful in the synthesis of phosphoranes,[3a,b] sulfuranes,[3c,d,e] persulfuranes,[3f] iodinanes,[3g] and periodinanes.[3h]



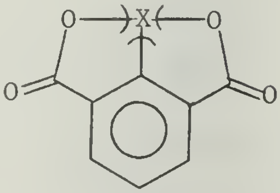
1a: $R=CF_3$
b: $R=CH_3$
X: I,S,P



2
X=I,S

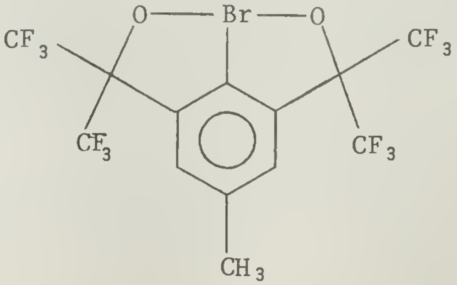


3a: $R=CH_3$, R'=t-Butyl; X=S
b: $R=CF_3$, $R'=CH_3$



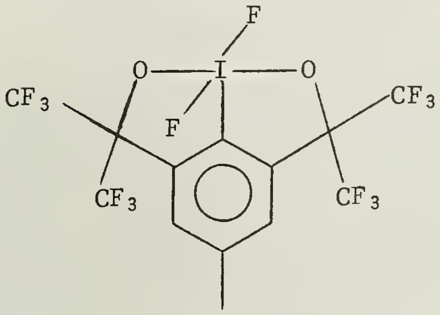
4
X=I,S

Recent availability of the precursors to compounds containing the tridentate ligand 3b has made possible the synthesis and isolation of the first tricoordinate organobrominane, 5, a 10-Br-3 species. Besides the effective electronegative apical oxygen atoms, this ligand also provides the effect of two five membered rings linking an apical and an equatorial position,[5] and the stabilizing Thorpe-Ingold effect of the gem-trifluoromethyl groups.[6] As a result of these stabilizing factors, 5 demonstrates a pattern of reactivity under a variety of conditions which is in marked contrast to the very unselective reactions of the only other 10-Br-3 species known. These inorganic brominanes are BrF_3, $Br(NO_3)_3$,[7] $Br(OSO_2F)_3$[8] and $Br(OSeF_5)_3$.[9] Brominane 5 behaves as an oxidizing reagent towards various substrates. Several reactions of 5 have been investigated.

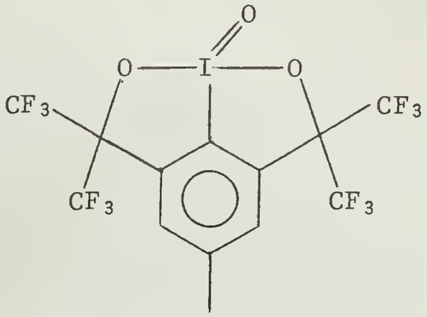


5

Stable aryldifluorodialkoxy periodinane 6 was also prepared and shown to be sublimable. It hydrolyzes to give iodinane oxide 7 which is a strong oxidizing reagent.



6



7

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$S_{RN}1$, THE MECHANISM AND SOME SYNTHETIC USES

Reported by Nancy J. Peacock February 16, 1981

The Mechanism. Nucleophilic substitution via radical anion intermediates was first outlined in the early 1960's by Nathan Kornblum.[1] In 1966, both Kornblum and Russell recognized that the reactions were actually chain processes and the original scheme was modified accordingly.[2] Since that time, this type of nucleophilic substitution has become well established and has been given the name $S_{RN}1$ denoting substitution, radical-nucleophilic, unimolecular.[3]

The general reaction sequence for the $S_{RN}1$ mechanism is outlined in Scheme I.

Scheme I

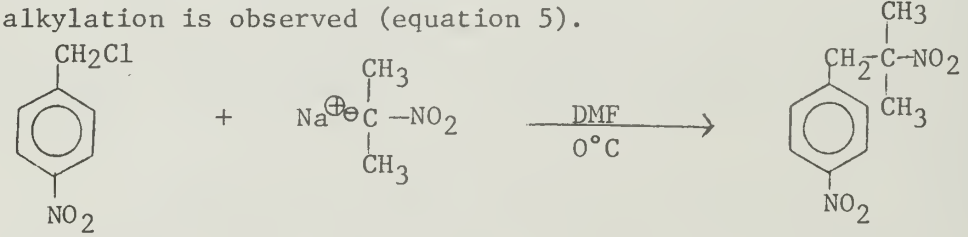
$$RX + Y^- (\text{or } e^-) \longrightarrow [RX]^{\cdot -} + Y\cdot \qquad (1)$$

$$[RX]^{\cdot -} \longrightarrow R\cdot + X^- \qquad (2)$$

$$R\cdot + Y^- \longrightarrow [RY]^{\cdot -} \qquad (3)$$

$$[RY]^{\cdot -} + RX \longrightarrow RY + [RX]^{\cdot -} \qquad (4)$$

In order to illustrate this mechanism more fully, an example from the work of Kornblum will be discussed.[4,1] When ρ-nitrobenzyl chloride is combined with the sodium salt of 2-nitropropane in DMF, a product resulting from carbon alkylation is observed (equation 5).

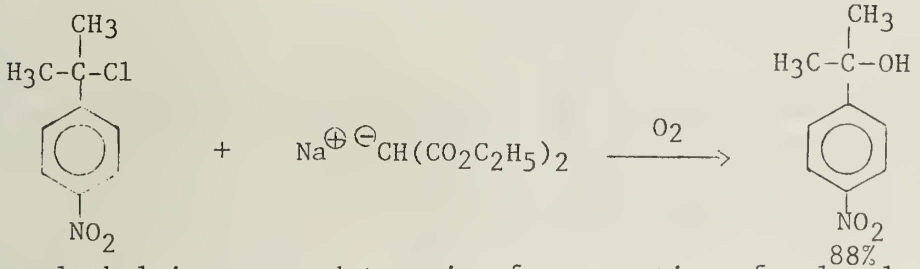


(5)

Until this time, this particular reaction was one of the few known instances where reaction of an aliphatic nitro compound with an alkyl halide gave carbon rather than oxygen alkylation. It was well known that the oxygen in an aliphatic nitro compound reacts as a nucleophile in S_N2 reactions with alkyl halides. (The product isolated from oxygen alkylation in equation 5 would be benzaldehyde). It was not clear as to why carbon alkylation should occur, but the factors favoring it were known. Carbon alkylation predominated (93-95%) if the benzylic portion was substituted in the para position by a nitro group, and if the leaving group was Cl, $N^+(CH_3)_3Cl^-$, or C_6H_5COO. A recent publication has shown that cyano groups on the aromatic ring are also effective in promoting carbon alkylation.[5] Nucleofugic groups such as I and Br gave 7 and 17% carbon alkylation with 81 and 65% oxygen alkylation respectively. Without the para nitro substituent, there was no leaving group effect and oxygen alkylation occured in 82-84% yield.[1]

In 1964 Kornblum proposed a radical mechanism to explain the above observations. The radical anion chain mechanism, postulated two years later, has been supported by many experimental observations. One of the most convincing is the inhibition of carbon alkylation with the addition of ρ-dinitrobenzene.[4,2a,c] Russell and Janzen[6] had previously shown that the radical anions of nitroaromatics spontaneously form in basic solution. Consequently, the addition of ρ-dinitrobenzene greatly inhibits the reaction by accepting an electron, thereby interfering with initiation step 1 and propagation step 4 (equations 1 and 4) of the reaction scheme. Similarly, radical scavengers such as di-tert-butyl nitroxide greatly inhibit the reaction.[7] The radical chain process is probably arrested after the second step (equation 2) at which point di-tert-butyl nitroxide reacts with the alkyl radical.

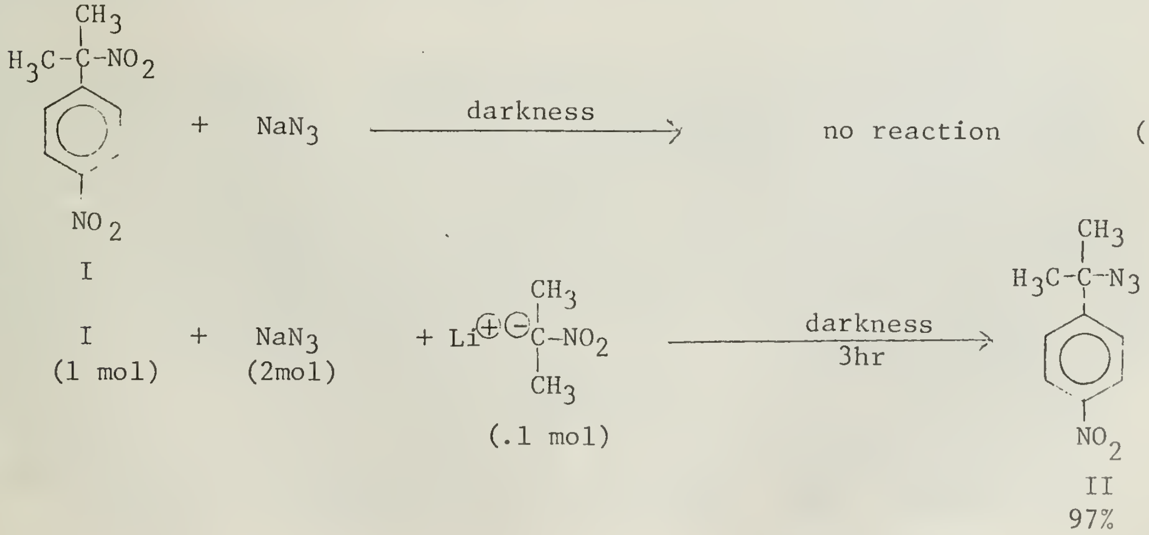
Molecular oxygen has also been shown to have an inhibitory effect on reactions proceeding via the $S_{RN}1$ mechanism.[2c,8,9] The magnitude of this effect is demonstrated in the ρ-nitrocumyl chloride reaction with sodiomalonic ester.[9] Under a nitrogen atmosphere, 90% of the carbon alkylated product is isolated, whereas in the presence of oxygen, ρ-nitrocumyl alcohol is obtained in an 88% yield (equation 6).



(6)

The alcohol is presumed to arise from reaction of molecular oxygen with the intermediate ρ-nitrocumyl radical.

Just as the $S_{RN}1$ mechanism can be inhibited by electron acceptors, it alternately may be initiated by electron donors or by light. Equations 7 through 9 exemplify these effects.



(7)

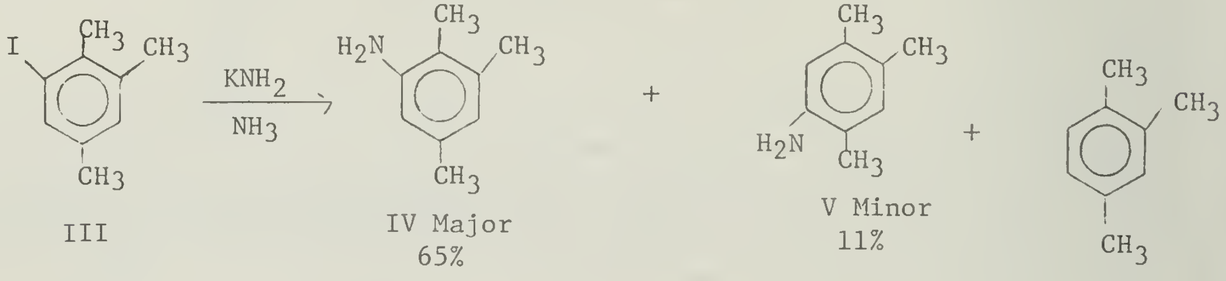
(8)

$$\mathrm{I} \quad + \quad NaN_3 \xrightarrow[10\ min]{h\nu} \mathrm{II}\ \ 94\% \qquad (9)$$

Even though α-ρ-dinitrocumene will not react with sodium azide after two days in the dark (equation 7), addition of a small amount of the lithium salt of 2-nitropropane causes reaction in three hours (equation 8).[10] In this case, the nitropropane anion is a better electron donor than sodium azide, so consequently it initiates the chain sequence. Once a ρ-nitrocumyl radical has been formed the sodium azide competes for it at least as well as the 2-nitropropane anion. Initiation may also occur when a one electron donor such as naphthalene sodium is added to the solution.[4]

In many instances, light acts to greatly enhance reactions proceeding via the $S_{RN}1$ mechanism.[2c,11] This observation is consistent with the proposed scheme, since light could act to cleave alkyl-halogen bonds or photostimulate electron transfer.[12,13] The magnitude of rate enhancement in the presence of light can be appreciated by comparing equation 7 with equation 9.

In 1970, Bunnett first reported that aromatic nucleophilic substitution proceeds via a radical anion chain mechanism.[3] The mechanistic scheme is identical to that of Kornblum's except that substitution occurs at an unsaturated carbon. Bunnett observed that iodo compound III does not undergo an anticipated aryne reaction to give a mixture of 5- and 6- pseudocumidine (V and IV respectively). Instead, reaction of KNH_2 in liquid ammonia gives mainly the products having retention of the original orientation (structure IV) with only a small amount of the cine-substitution product (structure V).



III

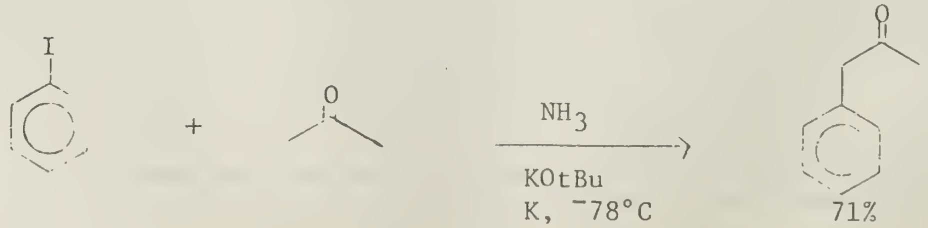
IV Major
65%

V Minor
11%

10%

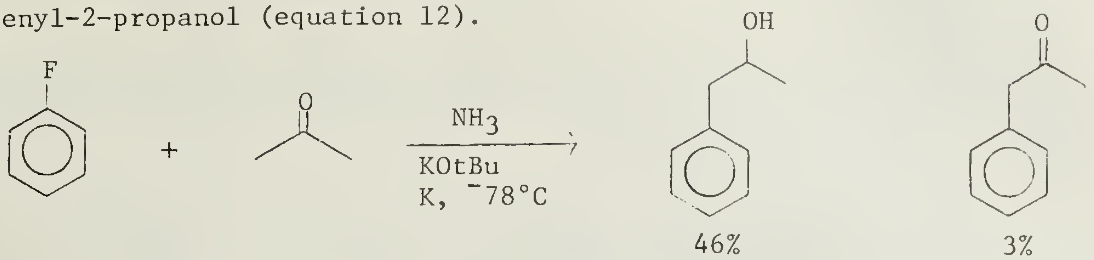
Bunnett carried out various experiments similar to those of Kornblum's in order to substantiate that the $S_{RN}1$ mechanism was indeed occurring in this case. In addition, this type of nucleophilic substitution can be accelerated by electron sources such as a cathode[14] or sodium or potassium metal.[3] Since 1970 Bunnett has shown that there are many instances of nucleophilic aromatic substitution, many of them compiled in 1978 by Bunnett[15] and Wolfe.[16] Some of them, particularly those of synthetic value, are discussed below.

Synthetic Utility. In 1972 the first work was published describing the arylation of acetone via the $S_{RN}1$ mechanism.[17] The acetone enolate was determined to be a nucleophile suitable to displace a nucleofugic substituent from an aromatic ring in the presence of solvated electrons. Several of the aryl substrates which gave substantial yields of phenylacetone were: C_6H_5Cl, C_6H_5Br, C_6H_5I, $C_6H_5NMe_3^+I^-$, and ρ-$CH_3C_6H_4Br$ (equation 11).



(11)

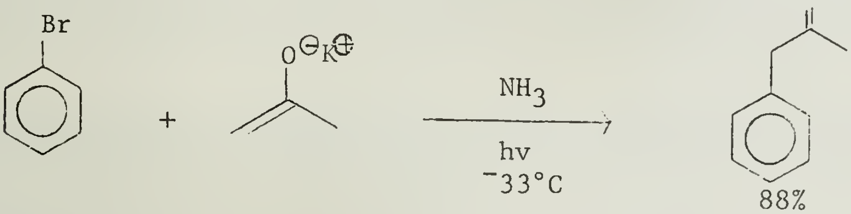
When fluorine was the nucleofugic substituent, the major product was 1-phenyl-2-propanol (equation 12).



(12)

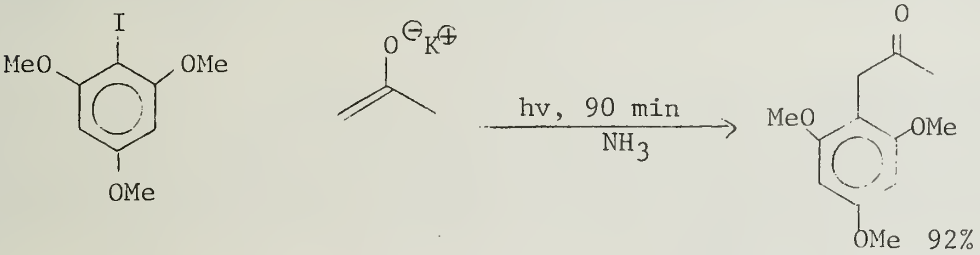
A recent publication by Bunnett considers solution mixing and an elaborated $S_{RN}1$ mechanism in order to rationalize these observations.[18]

Photoarylation of ketone enolate ions has been quite successful in producing high yields of arylated ketones (equation 13).[19]

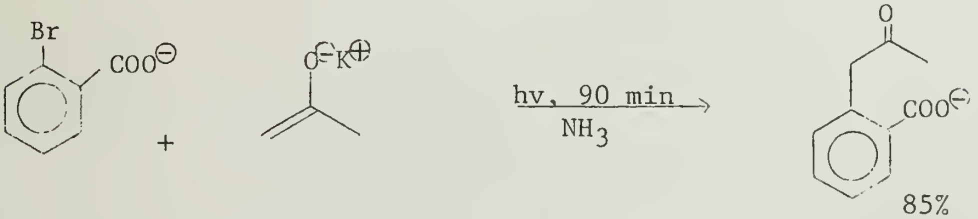


(13)

Many ring substituents render arylated acetones in very good yields, whereas a strong electron donor, such as $^-NH_2$, ortho or para to the nucleofugic group, or a meta-nitro group gives none of the desired products. Equations 14 and 15 represent two systems in which arylation occurs in high yield.



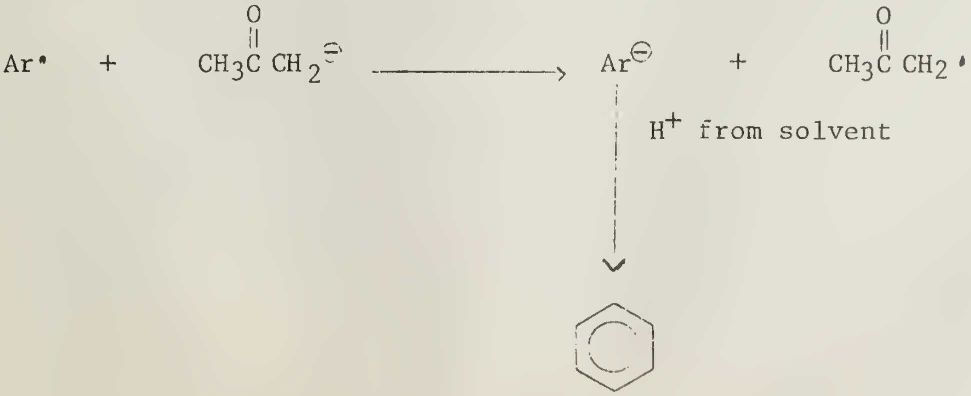
(14)



(15)

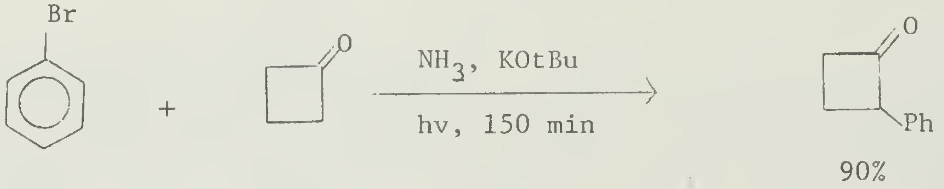
Bulky ortho substituents on the aromatic ring are not particularly favorable in that a large amount of dehalogenation product is formed. It has been suggested that the mechanism illustrated in Scheme II may be responsible.[20]

Scheme II


Ar•
+
$CH_3\overset{O}{\overset{\|}{C}}CH_2^{\ominus}$
$Ar^{\ominus}$
+
$CH_3\overset{O}{\overset{\|}{C}}CH_2•$
H^+ from solvent

Wolfe has reported that Ar· may abstract β-hydrogens if any are present on the ketone.[21]

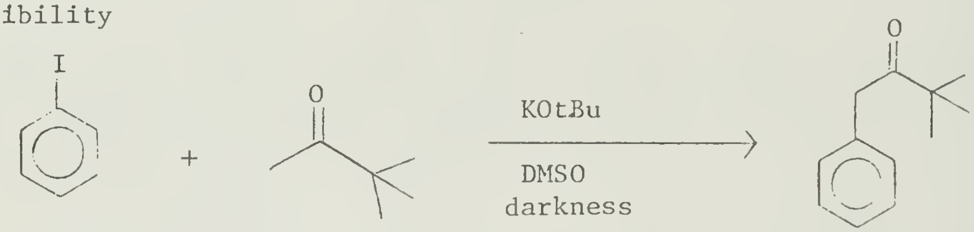
Cyclic ketones also have the potential of being arylated quite successfully.[19 b] Cyclobutanone reacts with bromobenzene to give the arylated product in 90% yield (equation 16).



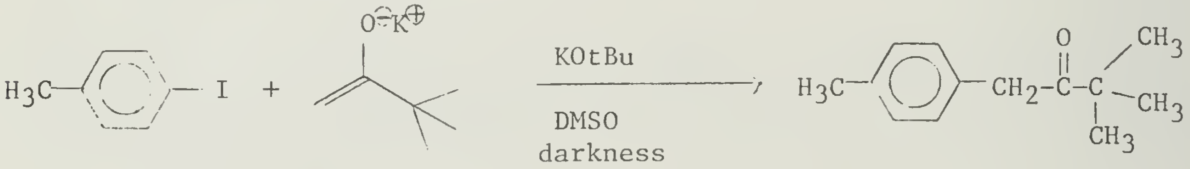
(16)

An interesting but unexplained observation was made regarding the arylation of cyclic ketones. Rings with an even number of carbon atoms give higher yields of the arylated ketone than those with an odd number of carbon atoms.

Some $S_{RN}1$ reactions of halobenzenes with ketone enolates can occur in complete darkness.[12] Pinacolone enolate ion will react with iodobenzene to give a nearly quantitative yield of arylated ketone (equation 17). The possibility of the aryne mechanism coming into play was excluded by considering the reaction of ρ-iodotoluene with pinacolone ion in which no cine-substitution was observed (equation 18). Substituent effects on the reactivity of aryliodides with pinacolone enolate ion are discussed in a recent article by Bunnett.[22]

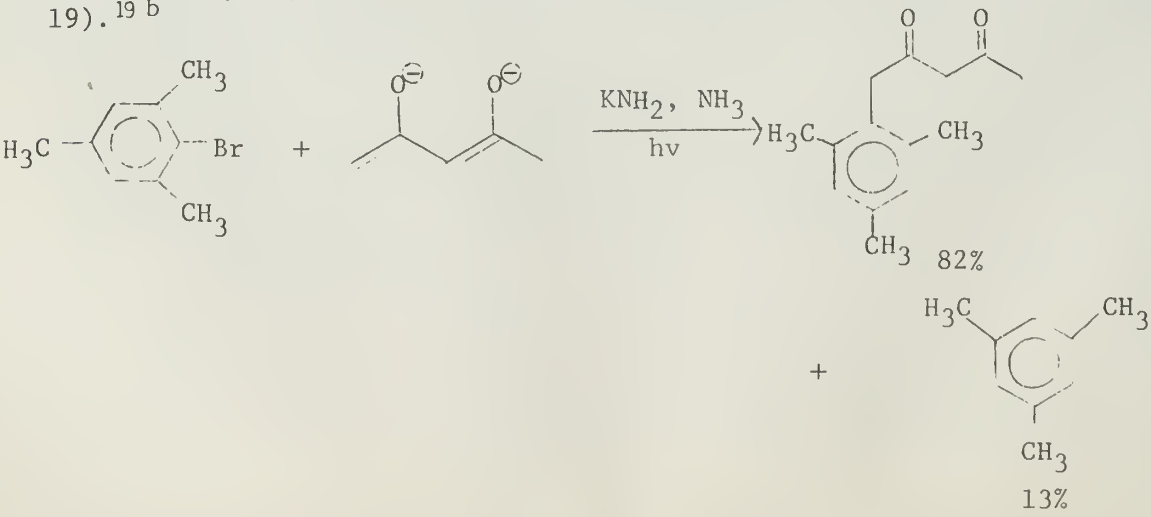


(17)



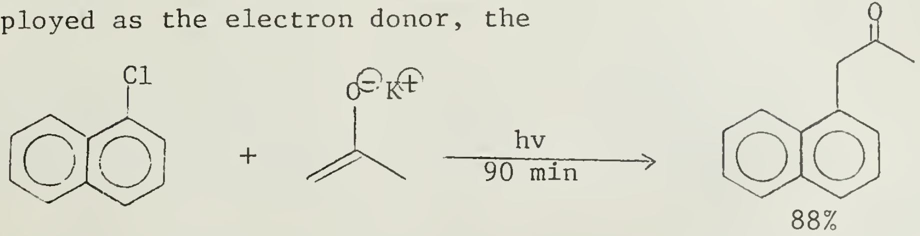
(18

Although the monoanions of β-dicarbonyl compounds have not been successfully arylated, the dianions make profitable nucleophiles (equation 19).[19 b]



(19)

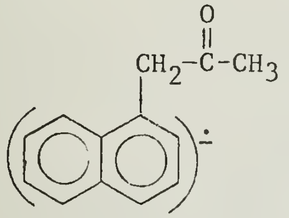
As one might predict, ketone enolate ions will react under photostimulation with 1-halonaphthalenes (equation 20). If potassium metal is employed as the electron donor, the



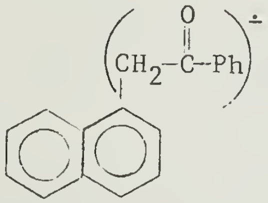
(20)

amount of 1-naphthylacetone afforded decreases, and a significant quantity of aromatic ring reduction products are isolated. These include 1,2 and 1,4 dihydro-1-naphthylacetone and 1,2,3,4-tetrahydro-1-naphthylacetone. The formation of reduction products has been rationalized by considering the energies of the molecular orbitals involved.[23,24]

Rossi has pointed out that when a phenyl radical, or as in this case a naphthyl radical, reacts with acetone enolate the extra electron must be located in either the naphthyl moiety or the carbonyl segment since these two are not in resonance with one another. The portion of the molecule in which the electron resides will be dictated by the relative energies of the LUMO's. In the radical anion of naphthylacetone the odd electron is located in the naphthyl ring, which has the lower energy LUMO (structure VI). In contrast, the radical anion of naphthylacetophenone is best represented by structure VII.[23,24]



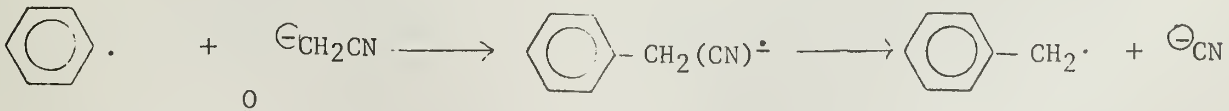
VI



VII

(21)

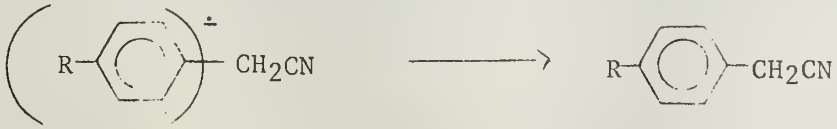
Likewise, the reaction of phenyl radical with cyano methyl anion results in a radical anion best represented by structure VIII owing to the lower energy cyano LUMO. In order to avoid bond cleavage as shown in equation 22, a substituent which will lower the LUMO of the aromatic moiety must be placed on the phenyl ring.[25,26] The $S_{RN}1$ mechanism thus provides a method of arylating cyano methyl groups (equation 23).



VIII

(22)

If R=⁻Ph, $-\overset{O}{\overset{\|}{C}}Ph$, then



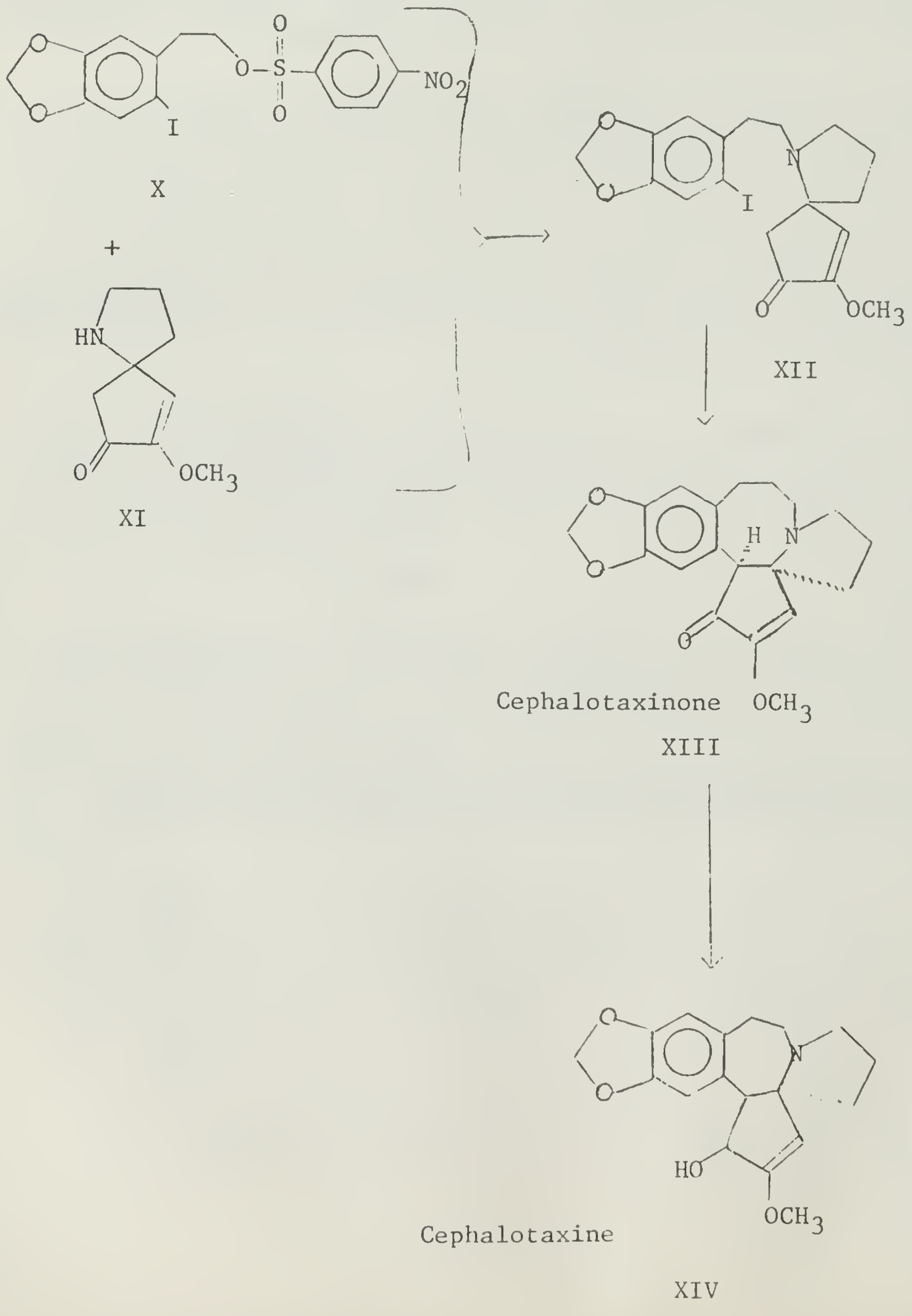
IX

(23)

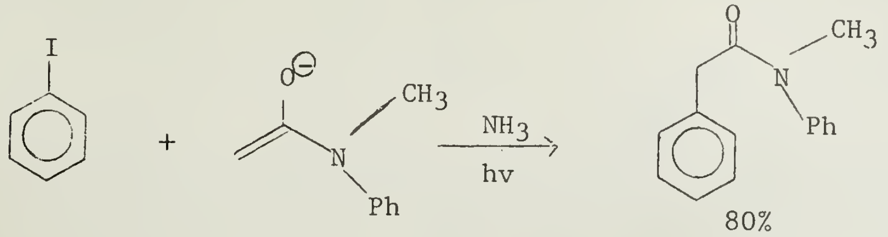
The sense of cleavage of many functional groups containing several different elements was determined by Bunnett in 1973.[27]

Semmelhack found the arylation of ketones via the $S_{RN}1$ mechanism to be quite useful in the total synthesis of Cephalotaxus alkaloids.[28] The general synthetic strategy involved the key intermediates shown in Scheme III. The most synthetically useful method of closing the seven membered ring was to irradiate XII in the presence of potassium tert-butoxide in ammonia for one hour. A 94% yield of (+, -) cephalotaxinone (XIII) was obtained. Similar systems investigated by Semmelhack have revealed some necessary restrictions if a high yield of substitution product is to be obtained.[29]

Scheme III

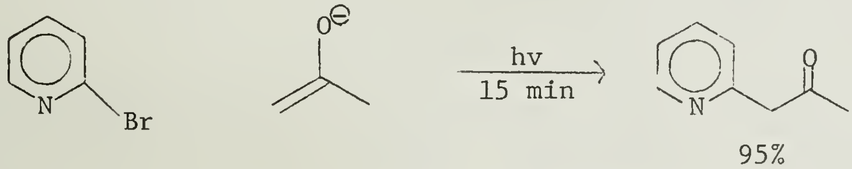


A reaction similar to the arylation of ketones is the arylation of N,N-disubstituted amides (equation 24).[30] Unsubstituted amides will produce no arylation owing to the acidity of the protons attached to nitrogen.



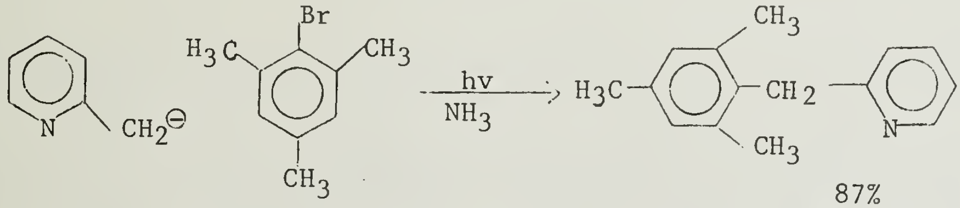
(24)

The $S_{RN}1$ mechanism is also capable of performing substitutions on heteroaromatic ring systems; for example, haloisoquinolines,[31] 2-chloroquinolidine,[32] and 2-bromopyridine[33] react similarly with acetone enolate in the presence of light as indicated by equation 25.



(25)

In contrast to equation 25, picolyl anions may act as nucleophiles and react with aromatic halides (equation 26).[34]



(26)

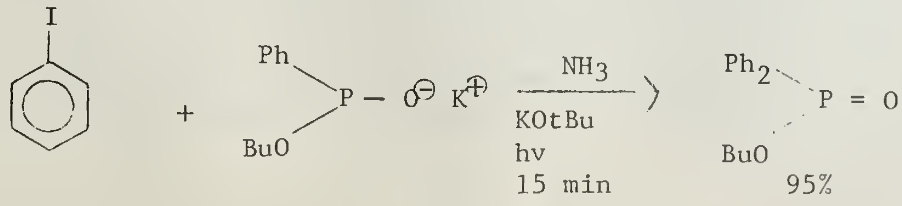
In 1972 Bunnett reported a two step synthetic transformation of phenols to anilines.[35] The phenol is first converted to the aryl diethyl phosphate ester, which is then taken to the aniline via an $S_{RN}1$ reaction (Scheme IV).

Scheme IV

$$\mathrm{ArOH} + \mathrm{NaOH} + (C_2H_5O)_2POCl \longrightarrow ArOPO(OC_2H_5)_2$$

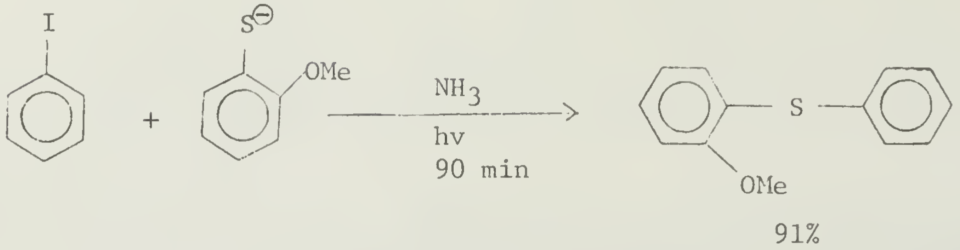
$$ArOPO(OC_2H_5)_2 + KNH_2 + K \longrightarrow \underset{56\text{–}78\%}{ArNH_2}$$

Another synthetically useful process is that of replacing an aryl halide with a phosphorous nucleophile (equation 27). The alkyl diaryl phosphinates are formed in yields of at least 85%.[36]



(27)

The $S_{RN}1$ mechanism provides a simple and synthetically useful process for synthesis of diaryl sulfides. Other methods require high temperatures for extended periods of time, or else explosive intermediates (equation 28).[37]



(28)

Many synthetically useful reactions, but perhaps less generally applicable, remain unmentioned. Some of the systems of both Kornblum and Russell provide for the synthesis of a variety of alkyl nitro compounds including aryl, ester, ketone, sulfone, sulfide, and cyano functionalities.[8,1b,38,11] Bunnett has arylated several carbanions[39] not mentioned above, including some vinyl halides[40] and thiophenes.[41] Bifunctional systems have also recently been studied.[42] The $S_{RN}1$ mechanism can provide an elegant synthetic route to many compounds which would otherwise be much more difficult to synthesize.

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A REDUCTION OF AROMATIC STABILITY IN FUSED HETEROAROMATIC SYSTEMS

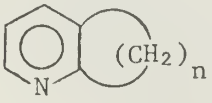
Reported by Joan Suits February 19, 1981

The stability of aromatic compounds has long fascinated organic chemists.[1] One way to understand the basis for this stability is by defining its limits: that is, finding out what can be done to reduce or nullify it. In 1930, Mills and Nixon theorized that the greater reactivity of indan compared to tetralin was due to bond-fixation in the aromatic ring, caused by the greater strain induced by the fused five-membered ring relative to that caused by the fused six-membered ring.[2] Although subsequent work has shown that bond-fixation does not occur in indan[3] or in the more strained benzocyclobutene[4] or benzocyclopropene[5], fused rings have been shown to perturb the aromaticity of benzene, as well as of other aromatic systems.[6] This perturbation manifests itself via changes in the spectral characteristics of the molecules and in the enhanced reactivity of the systems relative to that of their unstrained counterparts.[7] Still, considerable aromatic character remains.

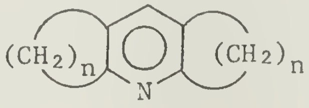
Aromatic systems containing a heteroatom (e.g. pyridine, quinoline, thiophene, etc.) are somewhat less stable than their carbocyclic counterparts.[8] It has been suggested[9] that these systems might therefore be more susceptible to the effects of fused rings, perhaps to the point of exhibiting bond fixation. In addition, the presence of the heteroatom provides for unique probes into the properties of such systems, supplementing those used to investigate analogous hydrocarbons. Thus, an examination of the structure and reactivity of such systems may yield further insight into aromaticity.

Aromatic systems have been characterized on the bases of reactivity and structure.[1b] Thus, the resonance energy of benzene is calculated[10] to be ca. 36 kcal/mol greater than that expected a priori for 1,3,5-cyclohexatriene, and there is no alternation in length of the carbon-carbon bonds. Similarly, the resonance energy of pyridine is estimated[8a] at 21 kcal/mol, and there is no alternation of bond length.[8b] X-ray crystallographic studies of fused aromatic systems show no alternation of bond lengths, although some distortions are present.[11] Unfortunately, such definitive structure work has not been performed on analogous heteroatomic systems.[12]

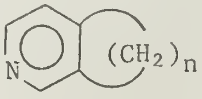
Some of the most conclusive work on the structure of fused aromatic systems has come from proton and carbon NMR. For example, in going from tetralin to indan to benzocyclobutene, a consistent variation in chemical shifts is observed.[4,13] Similar results are obtained for the fused pyridines I, II, III (n=2,3,4) and IV (n=3,4).[15-19]



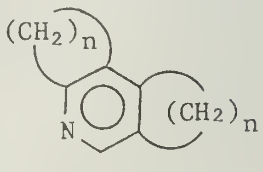
I



II



III



IV

These results show that as the size of the fused ring is decreased, the electron density at the carbon atoms *ortho* to a bridgehead increases, indicating a polarization of the C—H bond. In addition, the bridgehead carbons experience a decrease in electron density.[17] The ^{13}C—H coupling constant for the aromatic protons increases as strain in the systems increases, indicating[13,21] increased s character resulting from bond polarization. These results are consistent with the theory proposed by Streitwieser[9] that the strain caused by a small annelated ring induces a rehybridization of the bridgehead orbitals; a greater p character in the bonds to the fused ring causes a greater s character in the remainder of the bonds of the atom (fig. 1).

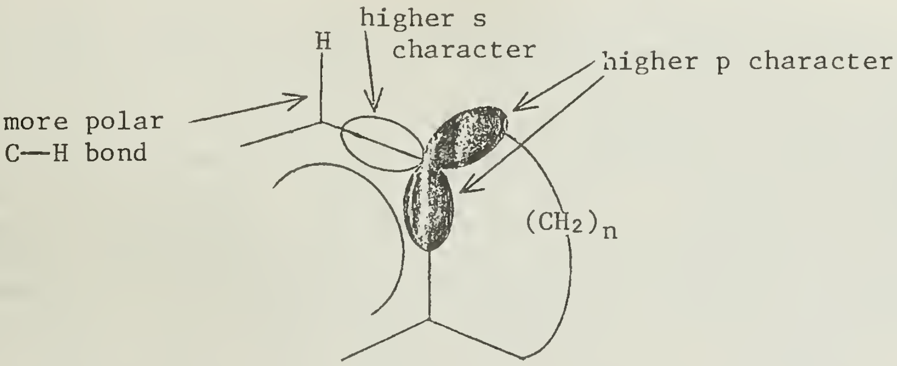


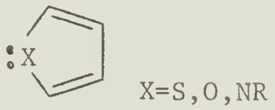
figure 1

Other theories have been proposed to account for the NMR trends, including geometric distortion and anisotropy effects such as perturbations to the aromatic ring current.[4] Although either of these might explain some of the results, the rehybridization theory gives consistently adequate results. However, it is quite possible that a combination of factors working together produces the observed trends.

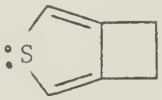
UV spectra of fused pyridines **I-IV** indicate[17] a slight shift of λ_{max} toward longer wavelengths as strain is increased, with a concomitant increase in ε. This has also been observed with some analogous carbocyclic systems,[22] and is also seen in fused quinoline,[23] quinoxoline,[24] and quinazoxoline[25] systems. The hypochromic shift has been interpreted[17] as an increase in the planarity of the molecule, leading to a better Franck-Condon overlap between the ground and the excited states. Implications for the aromaticity of such molecules are not clear.

A unique probe of the fused nitrogen-containing aromatic systems is the determination of pKa values, as related to half-neutralization potentials.[26] A generally observed trend is that as the strain of the fused system increases, the pKa decreases.[12,15-20,23-25] This is consistent with Streitwieser's hypothesis, since the lone pair of electrons on the nitrogen atom would be held more tightly if the atom was bonded to a bridgehead carbon using a bridgehead-carbon orbital of increased s character.

Although work with fused pyridines and related systems has shown that the aromaticity of such systems is perturbed by strain, evidence for bond localization[2] is hazy. However, some degree of bond alternation is implicated in fused systems containing the aromatic nucleus **V**.[9,27]



V



VI

The aromatic protons of the 3,4-fused thiophene **VI** exhibit shifts in the NMR[9] similar to those of the *ortho* aromatic protons of benzycyclobutene[4] and cyclobutapyridine.[20] In addition, treatment of **VI** with bromine afforded the tetrabromo addition product, in contrast to the reaction of bromine with thiophene or 3,4-dimethyl thiophene which gave the substitution product.[9] This result suggests that the strain of the fused ring is sufficient to reduce the tendency of the aromatic nucleus to reform the aromatic sextet. Similar studies with fused furans and pyrroles (**V**, X=O or NR) have not yet been performed, but NMR analysis[27] suggests similar distortions to the aromatic structure.

Thus far, it has not been possible to reduce aromatic stability to the point of bond fixation as envisaged by Mills and Nixon.[2] However, the results so far obtained suggest that work should be directed toward the construction of more highly strained fused systems, e.g. cyclopropapyridines. Besides providing information on the nature of aromatic stability, such compounds have potential use as synthetic intermediates[28] and as model compounds in mechanistic studies,[29] with widespread application in organic chemistry.

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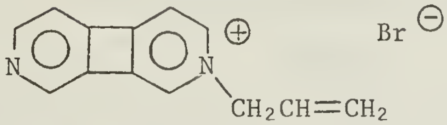

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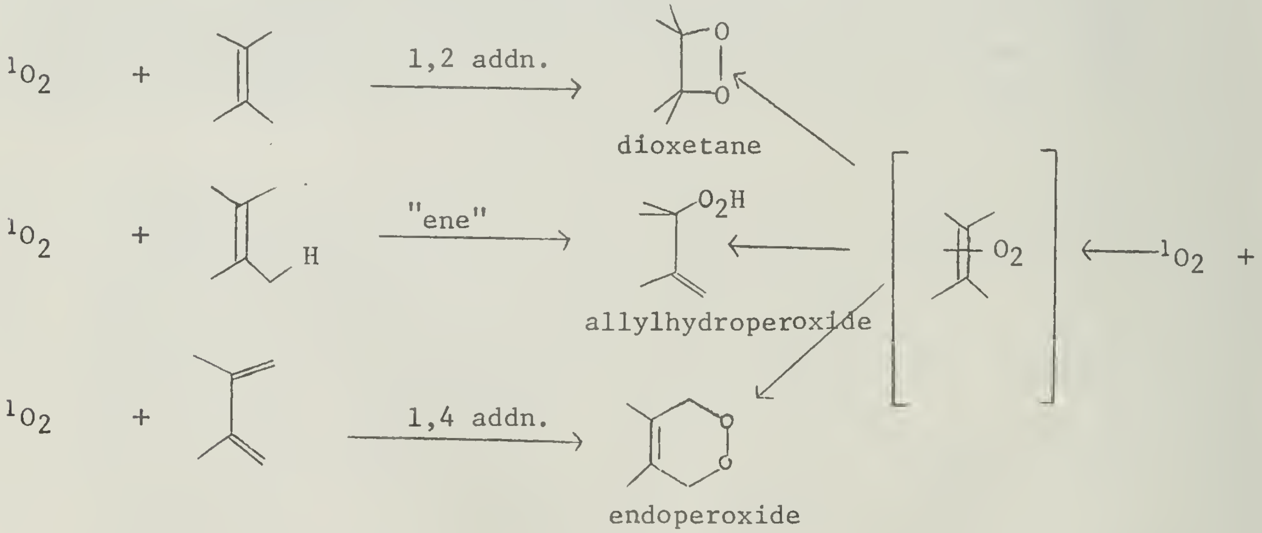
DIOXETANE FORMATION IN THE PHOTOSENSITIZED OXIDATION OF OLEFINS

Reported by Kenneth D. Wilson February 23, 1981

The photosensitized oxidation of olefins by molecular oxygen has been intensively studied for over thirty-five years.[1,2,3] A variety of chemical and physical methods were used to identify the lowest energy singlet state of molecular oxygen ($^1\Delta g$) as the active oxygen species in many of these oxidations.[1b] In some instances electron transfer and radical chain reactions have been observed to complicate the singlet oxygen ($^1O_2$) reactions.[1c,4] However, these competing reactions can usually be identified and prevented from interfering in $^1O_2$ photooxidation reactions.[1]

This review will examine the question of how dioxetanes are formed in the reactions of olefins with $^1O_2$ and what relationship dioxetanes have to the formation of other photooxidation products. Two basic types of hypotheses have been developed to answer these questions. One hypothesis views the formation of the three different primary products as occurring via three independent pathways, with each pathway having a unique transition state and intermediate(s).[1,2,3] Using known reactions as analogies, one could envision endoperoxide formation resulting from a $[\pi 4_s + \pi 2_s]$ cycloaddition, dioxetanes forming via a $[\pi 2_s + \pi 2_a]$ cycloaddition, and a concerted $[\pi 2_s + \sigma 2_s + \pi 2_s]$ "ene" mechanism giving allylhydroperoxides.

Scheme 1

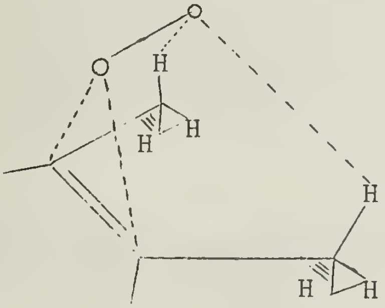


Although these mechanisms do not adequately explain the observed photooxidation chemistry, historically these reactions provided a starting point for the study of the individual reactions. The second hypothesis for the formation of the primary reaction products suggests that two or more product types may arise from a common transition state or intermediate. Although the support for this hypothesis is largely circumstantial, it is based upon the observation that many of the reaction parameters for the formation of the different photo-oxidation products are very similar.[1,2] Unfortunately, it has not yet been possible to distinguish between these mechanistic possibilities. Since only the absolute reaction activation energies and the relative difference in the activation energies of the product forming step are known, one cannot determine whether these energy differences occur in the rate determining step or in a subsequent product determining step.[5,6] Therefore the interception, identification and study of any reaction intermediates continues to be an area of active investigation.

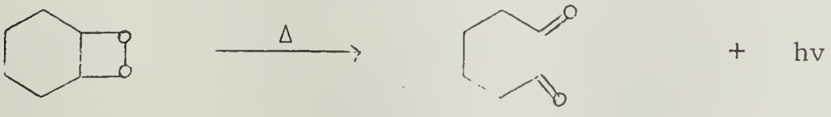
Proposed Mechanisms For Endoperoxide And Allylhydroperoxide Formation. A brief summary of the postulated mechanisms for the formation of endoperoxides and allylhydroperoxides is included because of their possible relationship to dioxetane formation. In his review of $^1O_2$-olefin photoxidation reactions, Frimer concluded that endoperoxides are probably formed via a concerted cycloaddition mechanism.[2] Paquette and coworkers recently studied the effects of the olefin frontier obital variations upon the stereochemistries and rates of $^1O_2$ additions.[7] Their results further support a concerted reaction mechanism.

In a very recent review Stephenson, Grdina, and Orfanopoulos concluded that a concerted "non-least-motion" mechanism was the simplest description for allylhydroperoxide formation via the "$^1O_2$-ene" reaction.[3] They point out that the transition state must have perepoxide-like symmetry and that the existence of an intermediate has not been ruled out (Figure 1).

Figure 1
Transition State Proposed for the "Ene" Reaction.



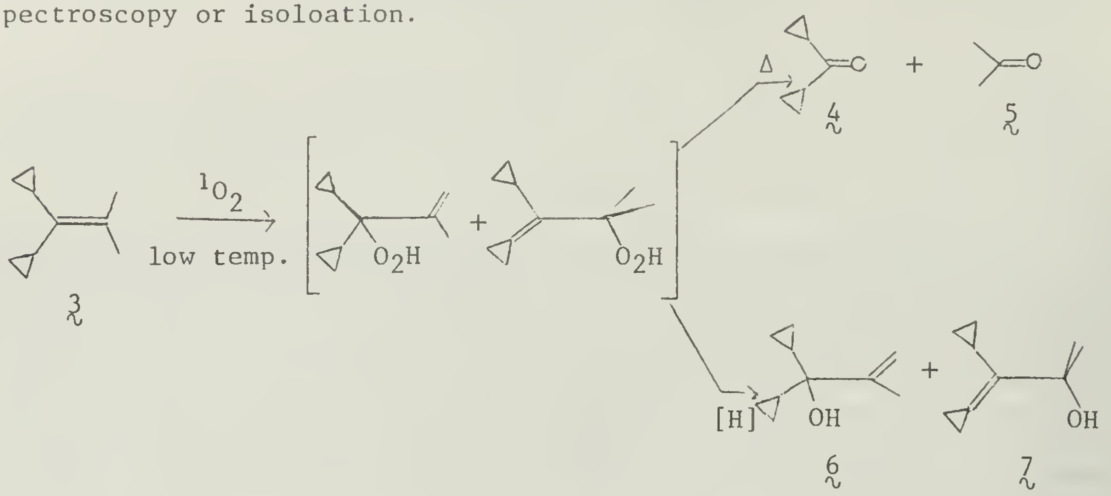
The Problem of Secondary Reactions In $^1O_2$ Photooxidations. Dioxetanes are thermally unstable and often difficult to isolate. Their formation is usually inferred from the isolation of characteristic types of carbonyl compounds such as **2**. These compounds are known to be the products of dioxetane **1** thermal decompositions.[1] However allylhydroperoxides **3**



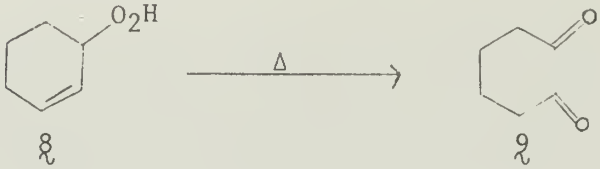
(1)

1 **2**

and 8 are also known to undergo thermal decomposition to carbonyls 4, 5 and 9 via a Hock type cleavage.[8,9] Therefore the peroxide source of the decomposition products must be verified by other means such as low temperature spectroscopy or isoloation.

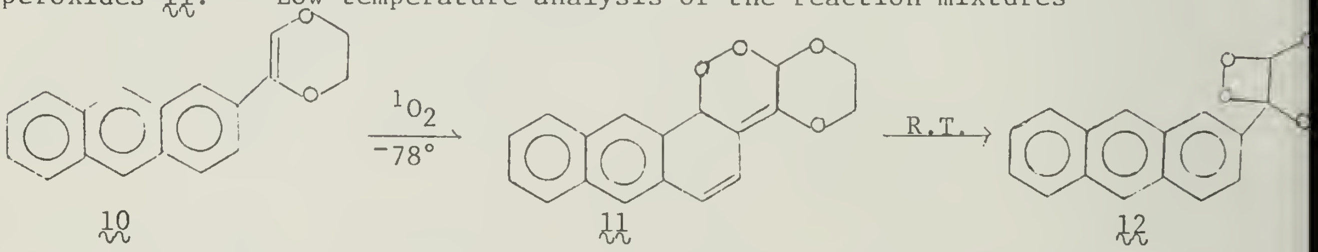


(2)



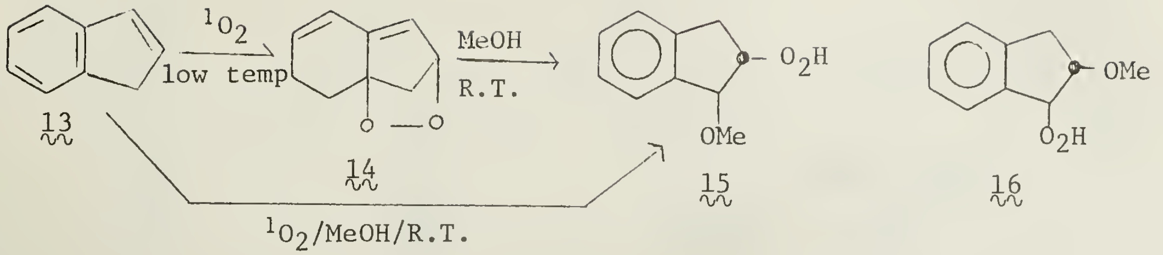
(3)

In addition to their formation as primary products, dioxetanes such as 12 are also known to form at ambient temperatures by rearrangement of endoperoxides 11.[10] Low temperature analysis of the reaction mixtures

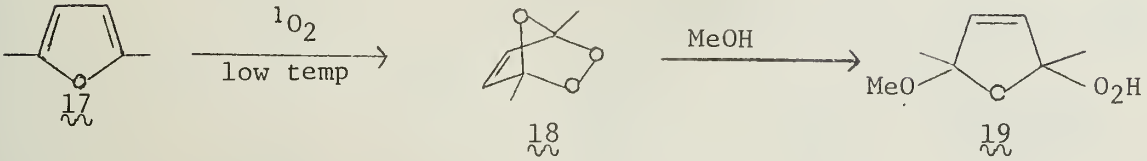


is usually used to determine whether the dioxetane products result from endoperoxide rearrangement.

A third important type of secondary reaction in $^1O_2$ photooxidations is the addition of protic solvents to the primary reaction products. Solvent incorporated hydroperoxides such as 15, 16, and 19 have been isolated in a number of $^1O_2$ photooxidation reactions. The presence of these products is often interpreted as evidence for the existence of zwitterionic reaction intermediates such as the 1,4-dipolarperoxide 44 and the perepoxide 45.[2,11] However, a careful reanalysis of these reactions revealed that this conclusion was incorrect.[12,13] When 13 and 17 are photooxidized at low temperatures the endoperoxides 14 and 18 are observed. Upon warming solutions of 14 and 18 the cleavage products are formed. When methanol is added to 14 and 18 the solvent addition products 15, 16, and 19 are obtained. These reactions demonstrated that the dipolar intermediates were not trapped and that the dioxetanes were not the primary photooxidation products.

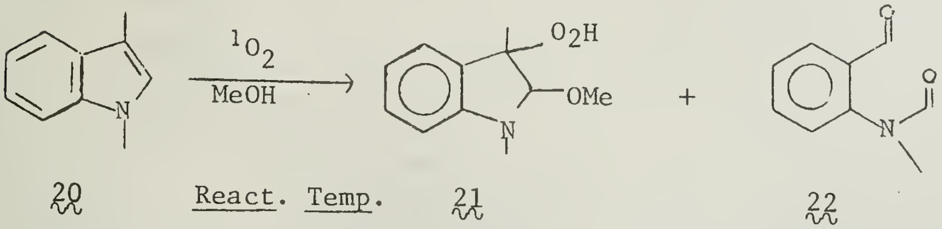


(5)



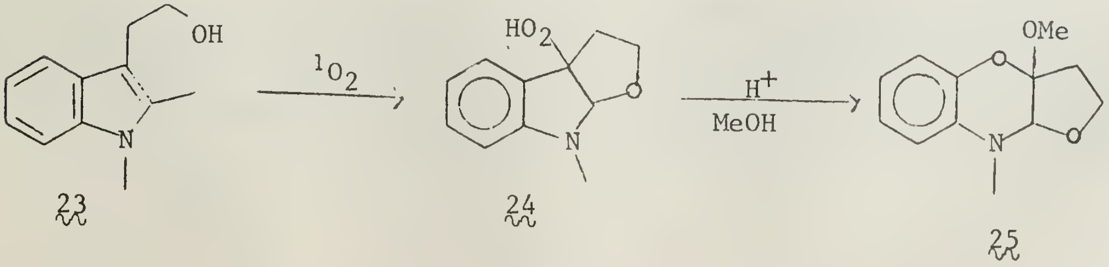
(6)

A number of recent papers reported the isolation of solvent containing products 21, 24, 29, 15, 16, and 33.[6,14] Interestingly the authors pointed out that the fraction of solvent containing products was greatest when the photooxidations were carried out at low temperatures. Saito stated that trapping of a transient dipolar intermediate would be more likely to occur at lower temperatures where rearrangement to product would be slower.[6b] This interpretation may be true but, following the low temperature reactions of 20, 23, and 13, the methanol is removed from the reaction mixture at 0°.[6,14] This reaction sequence is almost identical to that used to generate and trap the endoperoxides 14 and 18.[12,13] Without analysis of the reaction mixtures at low temperature, one cannot determine the source of the addition products in these reactions. Another criticism of the solvent

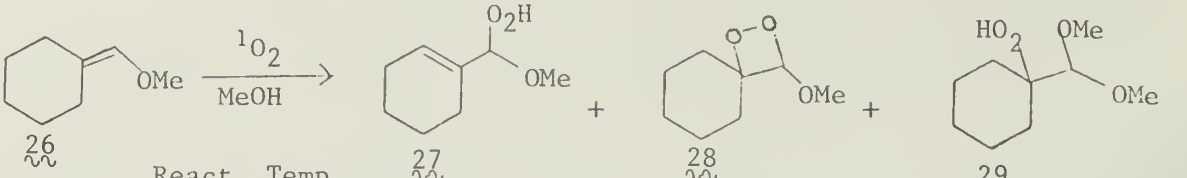


(7)

React. Temp.	21	22
-70	(97%)	(—)
R.T.	(—)	(90%)

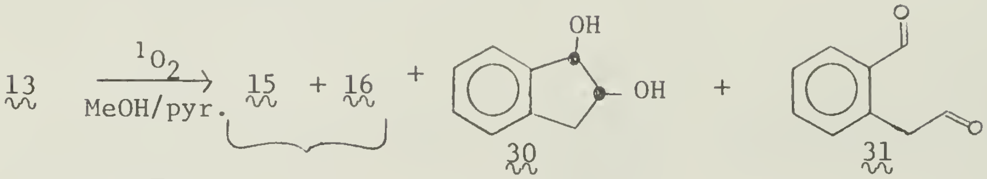


(8)



(9)

React. Temp.	27	28	29
$^-80°$	(9%)	(54%)	(37%)
20°	(32%)	(48%)	(20%)



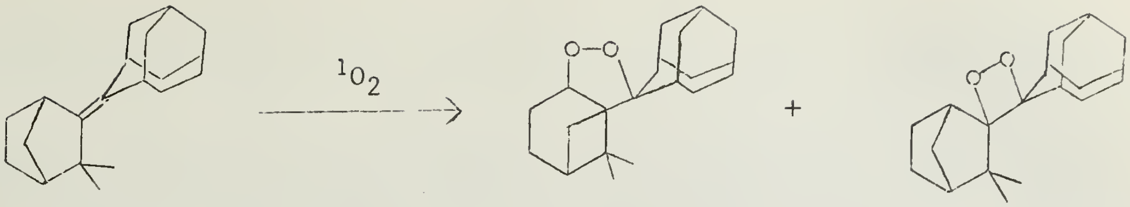
(10)

React. Temp.	15 + 16	30	31
$^-70°$	(73%)	(9.4%)	(–)
R.T.	(–)	21%	(<1%)

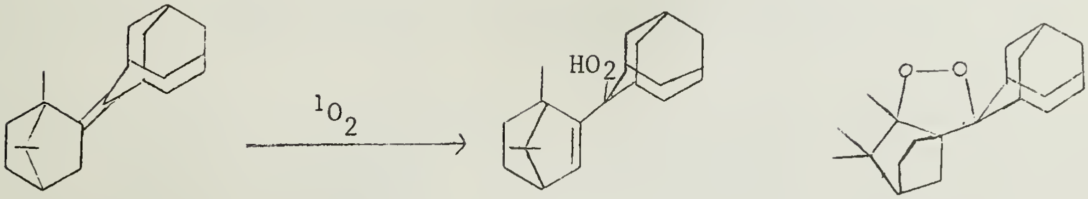
trapping experiments is that they fail to take into account the high reactivity of the "hot" primary photooxication product.[2] This question has been studied for the addition of carbenes to labeled vinyl cyclopropanes. In solution, it was found that the "cooling" of the biscyclopropanes was faster than the energy transfer from ring to ring.[15]

The Direct Formation of Dioxetanes From $^1O_2$ And Olefins. A number of careful studies have shown that dioxetanes are formed as primary $^1O_2$-olefin photooxidation reaction products.[6a,16,17,19] Dioxetane formation can compete with both "ene" and 1,4-addition reactions in electron rich olefins.[16,19] Dioxetane formation is also observed for olefins where the other reaction modes cannot occur.[16,17] Kinetic studies of $^1O_2$-olefin reactions give free energies of activation (based on loss of olefin) that are small ($\Delta G^{\neq}_{RXN} < 10$ kcal/mol) and entropy controlled ($\Delta H^{\neq} = 0.0$ to 0.5 kcal/mol and $\Delta S^{\neq} = {}^-18$ to $^-34$ eu).[5] The relative and absolute rates of dioxetane formation (versus "ene" reaction) show a moderate solvent dependence, however, this dependence does not strictly correlate with solvent polarity.[6a,17] The relative rates of dioxetane vs allylhydroperoxide formation also show a small temperature dependence with dioxetane formation being favored at lower temperatures.[6a,b] These differences in the relative rates of product formation as a function of temperature (and solvent) require that the activation energies ($\Delta G^{\neq}_{PROD}$) of the product forming steps be different. However, the range of energy differences observed for $\Delta\Delta G^{\neq}_{RXN}$ are as large as the differences observed between the $\Delta\Delta G^{\neq}_{PROD}$ values.[6] Since it cannot be shown from this data that $\Delta G^{\neq}_{RXN}$ and $\Delta G^{\neq}_{PROD}$ are of different magnitudes the existence of a reaction intermediate cannot be proven.

Evidence for an intermediate does come from other experiments. McCapra and Beheshti reported that the reaction of chemically generated $^1O_2$ with 32 and 35 occurs with rearrangement to give 33 and 37.[17] The ratio of dioxetane 33 to dioxetane 34 increases as the polarity of the solvent increases but reaches a maximum of 1:9 (Table 1). Additional



32 33 34 (11)

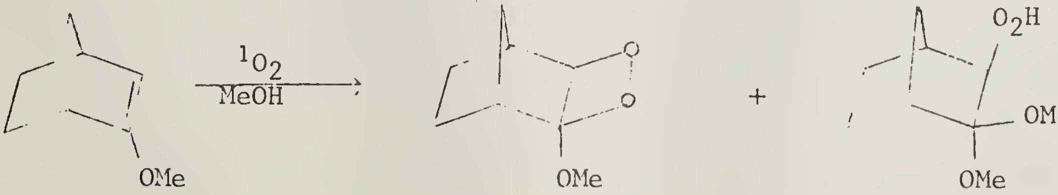


35 36 37 (12)

TABLE 1. Solvent dependence in the oxidation of 32

Solvent	Ratio 33:34
CH_2Cl_2	7:3
CH_3CN	3:7
acetone	1:9
methanol	1:9
methanol/water	1:9

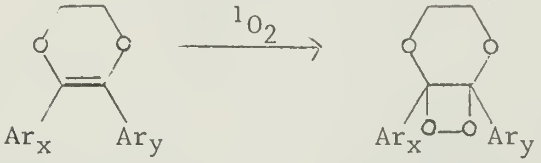
evidence for the existence of an intermediate comes from the following trapping studies. $^1O_2$ reacts with 2-methoxy-2-norbornene 38 in methanol to give a mixture of dioxetane 39 and hydroperoxydimethylacetal 40. Dioxetane 39 is stable in methanol under the reaction conditions.[18] Asveld and Kellogg



38 39 40 (13)

also reported methanol addition during the $^1O_2$ photooxidation of the vinyl ether 26. The peroxides 27 and 28 are stable in methanol and appear to be the primary reaction products, however it is not clear whether 29 results from trapping an "ene", 1,2-addition, or common reaction intermediate.[6a]

Two detailed studies have examined the question of charge distribution and isotope effects in the rate determining step of dioxetane formation.[16,19] Schaap and coworkers looked at how substituents affect the absolute $^1O_2$ reaction rates of a series of 2,3-diaryl-2-dioxenes 41 a-ℓ.[19] They found that a



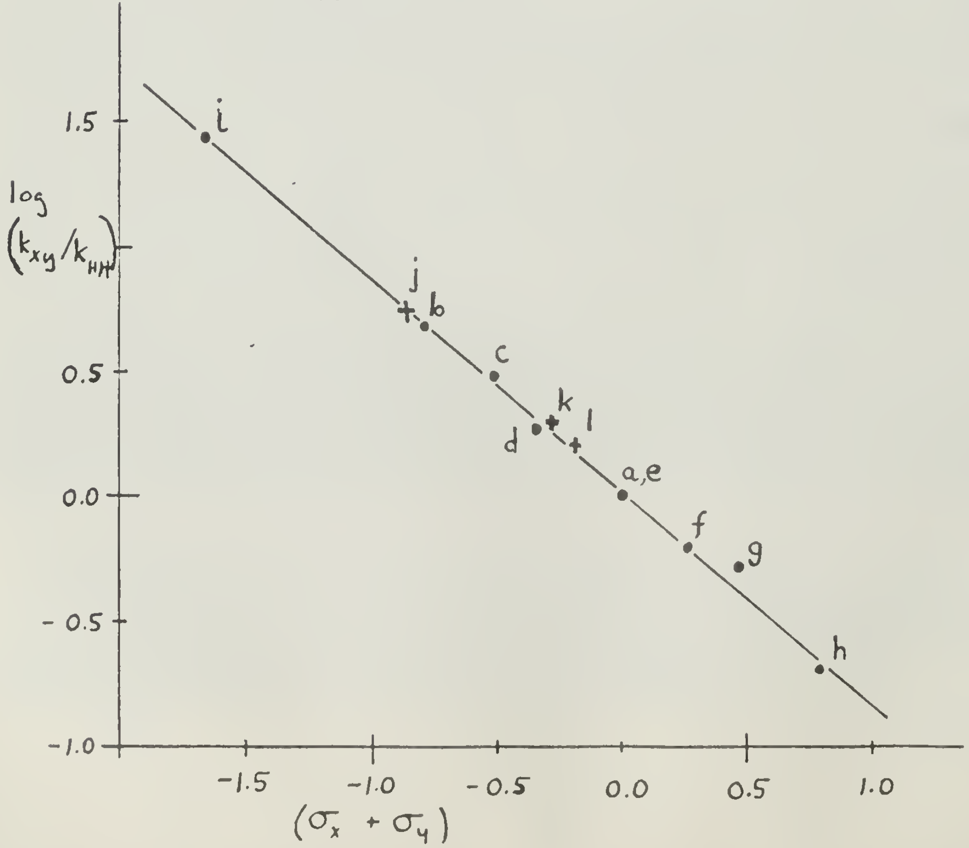
41 42

(14)

	x	y	cont	x	y
a	H	H	h	m-Cl	m-Cl
b	p-OH	p-OH	i	p-NMe$_2$	p-NMe$_2$
c	p-OMe	p-OMe	j	p-NMe$_2$	H
d	p-Me	p-Me	k	p-OMe	H
e	p-NHAc	p-NHAc	l	p-NMe$_2$	p-CN
f	m-OMe	m-OMe			
g	p-Cl	p-Cl			

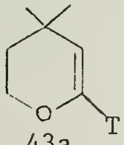
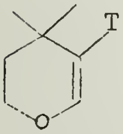
Figure 2

Plot of the log of the relative reaction rates versus the Hammett substitutient constants (σ_x + σ_y) for the reaction of 41 with $^1O_2$.



Hammett plot of the log $(k_{X,Y}/k_{H,H})$ versus $(\sigma_X + \sigma_Y)$ for dioxenes 41 a-i gave a $\rho = {}^{-}1.66$ (Figure 2). This value, as expected for the symmetrical dioxenes, was twice that reported ($\rho = {}^{-}.82$) for the substituted styrene derivatives.[20] Using the value $\rho = {}^{-}1.66$ and the combined substituent σ values the relative reaction rates for the unsymmetrical dioxenes 41 j-l (versus 41a) were calculated for transition states with either symmetric or unsymmetric charge distribution.[21] The results clearly show that charge is symmetrically distributed between the olefinic carbons. The experimentally determined $(k_{X,Y}/k_{H,H}) = 1.45$ for 41ℓ was almost identical to the value of 1.4 predicted for the symmetrical transition state (the unsymmetrical T.S. should have had a value of up to 3.4). In contrast to this result, Frimer and Bartlett found that the secondary kinetic isotope effects for the $^1O_2$ oxidation of 43a,b suggest that unequal rehybridization at the olefinic carbons occurs in the transition state (Table II).[16,22]

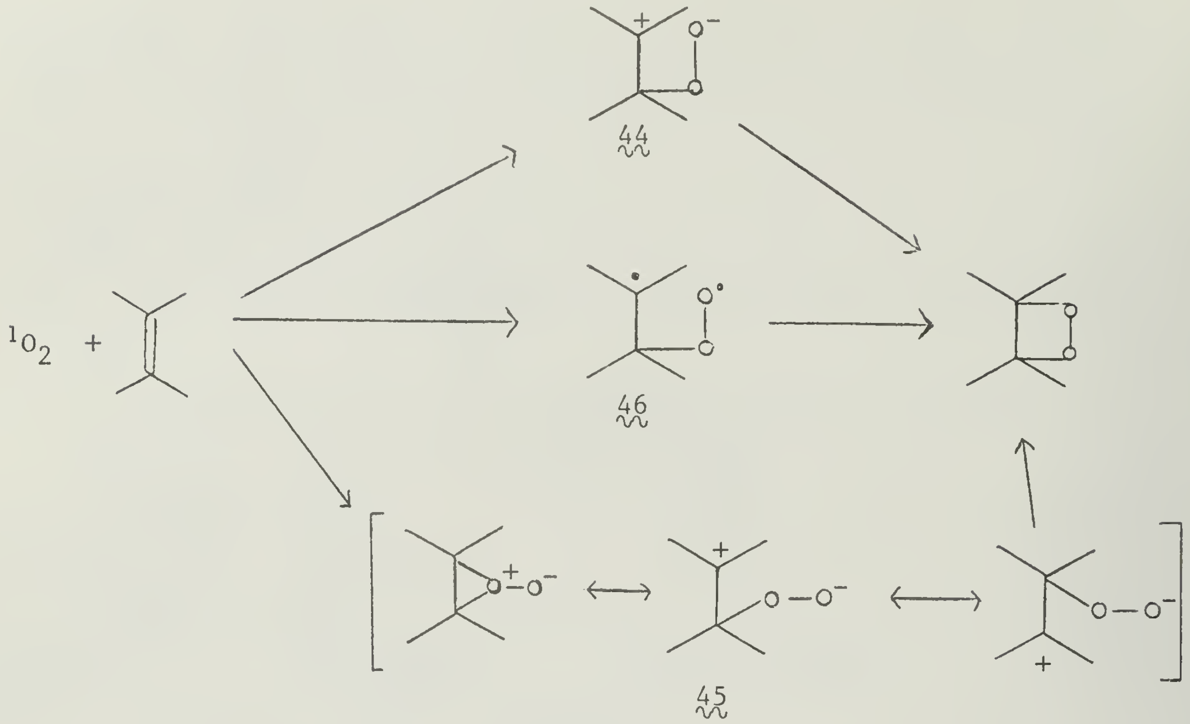
TABLE 2. Isotope Effects in the Photooxidation of 4,4-dimethyl-2,3-dihydropyran 43.

Compound	Kinetic Ratio	Value reported in Benzene	 Acetonitrile
 43a	k_H/k_T $(k_H/k_D)^a$	0.994±0.007 (0.996)	1.001±0.015 (1.001)
 43b	k_H/k_T (k_H/k_D)	0.897±0.002 (0.927)	0.897±0.006 (0.927)

(a) The corresponding k_H/k_D values for the experimental k_H/k_T values are given in parentheses.

Proposed $^1O_2$ Photooxidation Mechanisms. A concerted $[\pi 2_s + \pi 2_a]$ $^1O_2$ cycloaddition mechanism was proposed for the formation of dioxetanes; however, there is rather convincing evidence for an intermediate in this reaction. A number of M.O. calculations also support this conclusion.[11] One of the proposed models for this intermediate is a 1,4-zwitterionic peroxide 44. This zwitterion explains the observed solvent additions and the rearrangements of 32 and 35, but it seems unlikely that 44 would result from the charge-symmetric transition state required by Schaap's results.[19] The 1,4-diradical peroxide 46 is favored by Harding and Goddard.[11a] This model is consistent with both Schaap's substituent effects and the asymmetry in the transition state hybridization suggested by Frimer and Bartlett's results.[16] Radical rearrangements in systems such as 32 and 35 have not been documented. The third basic model for the $^1O_2$ photooxidation intermediate is a perepoxide 45.[11b,c] This intermediate is particularly intriguing because it is also the most likely intermediate for the "ene" reaction. Intermediate 45 readily explains the observed solvent addition and rearrangement reactions while

Scheme 2
Proposed Intermediates in Dioxetane Formation.



remaining consistent with the required charge symmetry of the transition states. The kinetic isotope effects reported by Frimer and Bartlett are inconclusive with regard to the formation of a perepoxide intermediate. Additional experiments will be needed to (1) define more fully the bonding and geometry of the reaction intermediate(s); (2) determine the nature of the observed solvent effects and (3) discover what relationships exist between the intermediate in dioxetane formation and the formation of the 1,4-cycloaddition and "ene" products.

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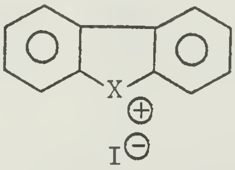
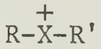
21. $k_{x,y}/k_{H,H} = 0.5 \times 10^{-1.66(\sigma_x + f\sigma_y)/(1 + f)} + 0.5 \times 10^{-1.66(\sigma_y + f\sigma_x)/(1 + f)}$, where f is a correction factor for the σ effect at the β carbon and x and y are the aryl substituents on **41**.[19]
22. Similar effects were found for the secondary isotope effects in the "ene" reaction of 4-methyl-2,3-dihydropyran.

THE FIRST REPORT OF A PERIODONIUM SALT, A STABLE 10-I-4 SPECIES

Reported by Daniel Dess February 26, 1981

Halonium ions, 8-X-2 species,[1] have been known for years.[2a,b] Halonium ions containing chlorine,[2a,3] bromine[2a,3] and iodine[2a,b] have been synthesized. They are stable isolable compounds with well characterized reactivities and physical properties. Examples are listed below.





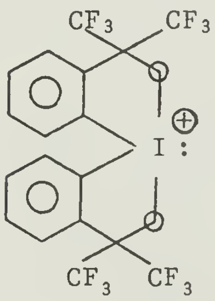
$$R-\overset{+}{X}-R'$$

	X
1a	Cl
b	Br
c	I

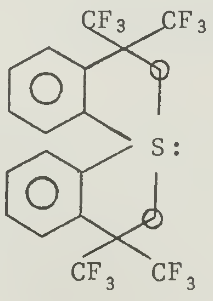
	R	R'
2a	alkyl	alkyl
b	aryl	alkyl
c	aryl	aryl

Although dialkyl and aryl-alkyl halonium ions are known,[2a,4] the diaryl ions are the most readily synthesized and isolated. These compounds have some synthetic use as arylating agents.[2a,b,5]

Recently the first stable isolable perhalonium[6,7] ion has been synthesized. The hypervalent 10-I-4 species, **3**, is isovalent with the known hypervalent compounds of sulfur[8] and phosphorous,[9] **4** and **5**. The stability of the periodonium ion was predicted based on analogy with **4** and **5**. An



3



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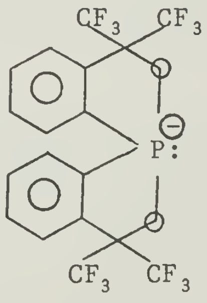

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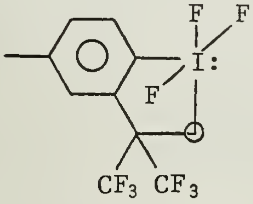
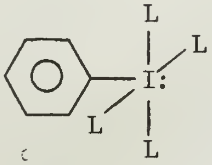
X-ray crystallography structure determination has not only confirmed the structure of **3**, but has also provided data for comparison with other hypervalent compounds.

The periodonium ion is stable toward water in solution in acetonitrile, acetone, and tetrahydrofuran. This reactivity is similar to that of the heterocyclic periodinane, **6**.[10] It is in

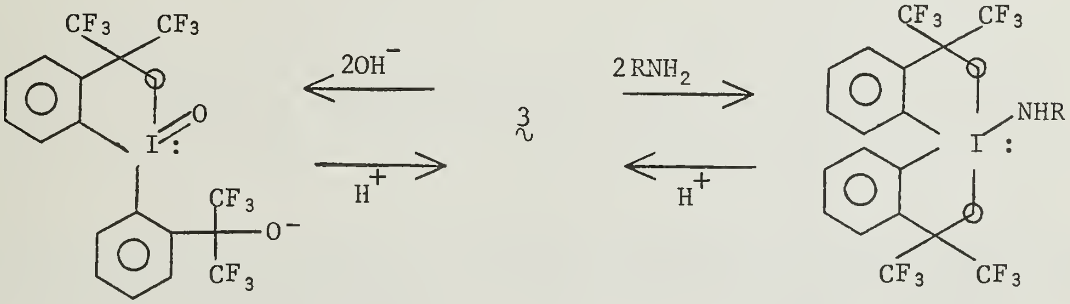


6



	L
7a	F
b	OOCCF$_3$

marked contrast with the reactivity of **7**a,[11] **7**b,[12] and IF$_5$.[13] These compounds are hydrolyzed rapidly on exposure to atmospheric moisture. Iodine pentafluoride reacts violently with organic substrates. The periodonium ion reacts with two equivalents of hydroxide to give an iodinane oxide, **8**. The reaction is reversed by addition of acid. Two equivalents of amine react reversibly with **3** to give **9**. Further studies on the properties of the periodonium ion and its derivatives are under way.



8 **9**

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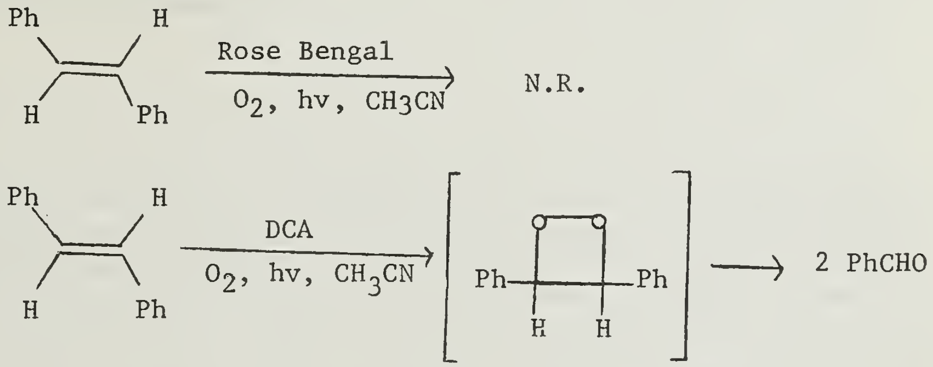
Electron Transfer Photooxygenation Mechanisms

Reported by Alan Schrock March 2, 1981

Much attention has been focused on singlet oxygen ($^1O_2$) and its photosensitized reactions with organic compounds.[1] Recently, several electron deficient sensitizers have been found to promote the oxygenation of electron rich olefins which, with standard singlet oxygen techniques, give no oxygenated products. Mechanisms involving electron transfer have been proposed to account for this difference in reactivity. These electron transfer photooxygenation mechanisms will be the topic of this report.

Electron rich olefins such as trans-stilbene, (TS), do not react with singlet oxygen generated by rose bengal sensitization.[2] When 9,10-dicyanoanthracene, (DCA), is employed as the sensitizer, 2 moles of benzaldehyde are found as products. Benzaldehyde would be the result of the decomposition of the intermediate dioxetane. (Scheme I)

Scheme I



Foote has proposed an electron transfer mechanism to explain these results.[2] The photo excited dicyanoanthracene reacts by electron transfer with the donor olefin; the radical ions then diffuse apart in polar solvents. The dicyanoanthracene radical anion reduces oxygen to superoxide ($O_2^{\overline{\cdot}}$) regenerating DCA in the ground state. Superoxide then reacts with the olefin radical cation to produce the oxygenated product. (Scheme II)

Scheme II

$$DCA \xrightarrow{hv} DCA^*$$

$$DCA^* + O \longrightarrow DCA^{\overline{\cdot}} + D^{+\cdot}$$

$$DCA^{\overline{\cdot}} + {}^3O_2 \longrightarrow DCA + O_2^{\overline{\cdot}}$$

$$D^{+\cdot} + O_2^{\overline{\cdot}} \longrightarrow DO_2$$

The central feature in this mechanism is the electron transfer from the donor olefin to the sensitizer for the production of radical ions, rather than energy transfer from the excited state sensitizer to molecular oxygen for the production of singlet oxygen. From studies of the photophysics of these systems,[3] Foote has shown that electron transfer from the olefin to the cyanoaromatic sensitizer occurs. The fluorescence of the cyanoaromatic sensitizers was found to be quenched by electron rich olefins Weller has shown that the free energy involved in electron transfer fluorescence quenching can be calculated from equation 1.[4] In equation 1,

$$\Delta G = 23.06\,(E_{ox} - E_{red} - E_{col} - \Delta E_{o,o}) \qquad (1)$$

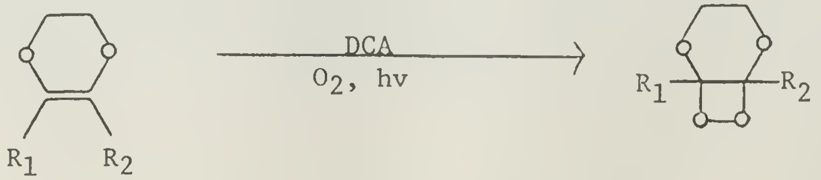
E_{ox} is the oxidation potential of the quencher, E_{red} is the reduction potential of the sensitizer, E_{col} is the coulombic term (0.06 ev in acetonitrile), and $\Delta E_{o,o}$ is the electronic excitation energy of the sensitizer. The quenching rate constants were found for a series of olefins from a Stern Volmer analysis, a plot of fluorescence intensities versus quencher concentrations. When the free energies for electron transfer were plotted against the quenching rate constants, the resultant curve was found to fit one calculated by Weller for these processes. Also, the dependence upon solvent polarity for exciplex emission was shown to occur as calculated for electron transfer processes. These photophysical results were taken as strong evidence in support of the electron transfer generating the sensitizer radical anion and the olefin radical cation.

Foote later reported the direct observation of the generation of radicals by laser flash photolysis.[5] With either 9,10-dicyanoanthracene or 9-cyanoanthracene and trans-stilbene, irradiation of the sensitizer in nitrogen purged acetonitrile generated $TS^{+\cdot}$ and the sensitizer radical anion. The transient decay rate for the sensitizer radical anion increases upon going from nitrogen purged to air saturated acetonitrile. Oxygen saturation removes the sensitizer radical anion absorption with only a small effect on the $TS^{+\cdot}$ absorption.

The reduction potential, E_{red}, for 9,10-dicyanoanthracene is $^{-}0.82$v and $^{-}0.57$v for oxygen. Hence, electron transfer from $DCA^{-\cdot}$ to $^{3}O_2$ should have a free energy of $^{-}5.0$ kcal/mole, as calculated from Wellers' equation. These two facts strongly suggest that the cyanoaromatic radical anions reduce molecular oxygen forming superoxide, the third step in the oxygenation mechanism.

Schaap observed by esr the generation of $DCA^{-\cdot}$ upon irradiation of a solution containing 1,1-diphenylethylene and DCA in deoxygenated acetonitrile, acetone, and methylene chloride.[6] With 2-methyl-9,10-dicyanoanthracene as sensitizer, Schaap oxygenated a series of olefins and obtained the corresponding dioxetanes. (Scheme III)

Scheme III



I

a $R_1 = R_2 = p - \text{MeOPh}$
b $R_1 = R_2 = 2 - \text{naphthyl}$
c $R_1 = \text{Ph},\ R_2 = H$

Schaap also investigated the last step in Foote's mechanism, the reaction of superoxide with the olefin radical cation. A competitive experiment was undertaken to show that it is indeed superoxide and not molecular oxygen that is acting as the oxygenating species.[6] The radical cation of alkene Ia was generated chemically and a solution of superoxide was added. The solution of $Ia^{+\cdot}$ rapidly decolorized indicating the end of the reaction. Molecular oxygen was bubbled through a similar solution with the reaction requiring 30 times as long to be completed. The yield of products was greatly reduced when molecular oxygen was used to quench the radical cation as compared to reaction with superoxide. The reduced rate of reaction with $^3O_2$, along with the reduced yields of oxygenated products, strongly indicates the intermediacy of superoxide.

Foote determined the quantum yield for the photooxygenation of a typical system, 1,1-diphenylethylene and 9,10-dicyanoanthracene, in acetonitrile, and found it to be 0.8. This indicates that the back electron transfer in the initial exciplex or in the solvent separated ion pairs is a relatively unimportant path in the reaction.

In cases where the substrate is susceptible to singlet oxygen addition, an addition step in the mechanism, the annihilation of superoxide and the substrate radical cation to form singlet oxygen and ground state substrate, must be considered. (Scheme IV)

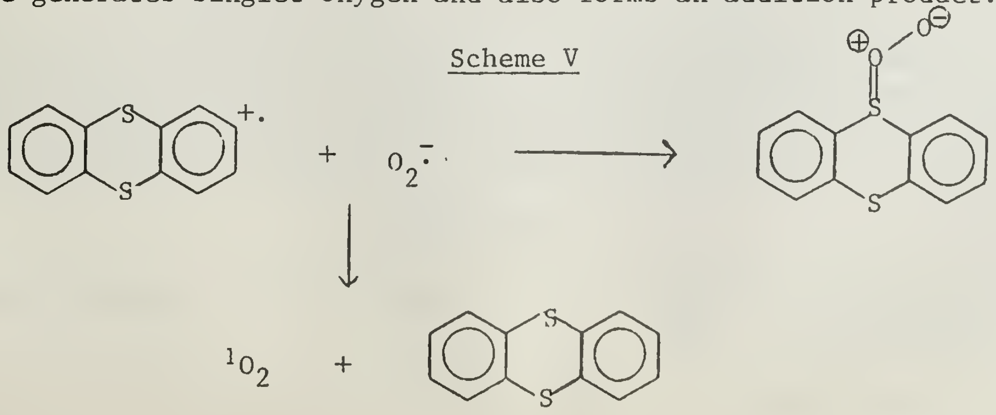
Scheme IV

$$D^{+\cdot} + O_2^{\overline{\cdot}} \longrightarrow {}^1O_2 + D$$

Bard has shown that superoxide and either ferrocinium ion or 1,3-diphenylisobenzofuran (IBF) radical cation annihilate to produce singlet oxygen.[8] The ion radicals are produced in the same solution by repeatedly pulsing the electrode potential from the reduction potential of oxygen to the oxidation potential of the substrate. With both ferrocene and IBF in solution, ferrocene can be oxidized without affecting IBF by controlling the electrode potential, since the oxidation potential of ferrocene is lower than that of IBF. When the electrode potential was pulsed and both ferrocinium ion and superoxide were produced, IBF was converted to o-dibenzoylbenzene. When no ferrocenium ion was produced, very little o-dibenzoylbenzene was found. This shows that the reaction of singlet oxygen with IBF is required to produce o-dibenzoylbenzene. The efficiency of formation of singlet oxygen was estimated to be 4% by the total number of faradays required to produce a known amount of o-dibenzoylbenzene.

Ando has shown that the reaction of thianthrene radical cation and superoxide generates singlet oxygen and also forms an addition product. (Scheme V)

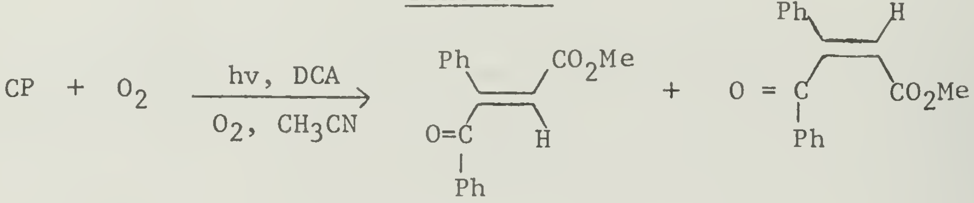
Scheme V



In this case, singlet oxygen was monitored by its dimole emission, the emission resulting from the annihilation of two singlet oxygen molecules. An estimation of the yield of $^1O_2$ was 100%.

The mechanism for the cyanoaromatic sensitized photooxygenation of electron rich olefins is well supported. However, there are cases in which the initial electron transfer from donor to excited state sensitizer is followed by a chain mechanism with quantum yields greater than 10. For example, when DCA is irradiated in oxygen saturated acetonitrile with methyl-1,2-diphenyl-3-carboxylate, CP, a mixture of oxygenated products are found with a quantum yield of 20 for the disappearance of CP.[10] (Scheme VI)

Scheme VI



major products

Fluorescence quenching and exciplex emission studies show that electron transfer is forming both $DCA^{\overline{\cdot}}$ and $CP^{+\cdot}$. However, it appears that $CP^{+\cdot}$ is reacting with molecular oxygen in a chain mechanism. It is also possible that superoxide reacts with $CP^{+\cdot}$ as well. At this point, the oxygenation mechanism is not well understood.

One final example is the slow photooxygenation of trans-stilbene when sensitized by methylene blue, MB^+.[11] In this case, other singlet oxygen sensitizers such as rose bengal fail to give any reaction. Trans-stilbene is found to quench the fluorescence of MB^+ but not that of rose bengal. The free energy change for the electron transfer was calculated to be $^-3.7$ kcal/mole for MB^+; the ΔG for electron transfer to rose bengal is endergonic. The production of superoxide from the reduction of oxygen by MB° is not expected since the ΔG is calculated to be strongly endergonic. Accordingly, it was suggested that molecular oxygen is reacting with $TS^{+\cdot}$, leading to the oxygenated products. (Scheme VII)

Scheme VII

$$MB^+ \xrightarrow{h\nu} \overset{*}{MB}{}^+$$

$$\overset{*}{MB}{}^+ + TS \longrightarrow MB^{\circ}\cdot + TS^{+\cdot}$$

$$MB^{\circ}\cdot + TS^{+\cdot} + O_2 \longrightarrow MB^+ + 2\ PhCHO$$

As these examples show, simply because a dye sensitized photooxygenation is performed, the reacting species need not be singlet oxygen. The ongoing research in the non-singlet oxygen mechanisms of dye sensitized photooxygenations will lead to a better understanding of the chemistry involved in this field.

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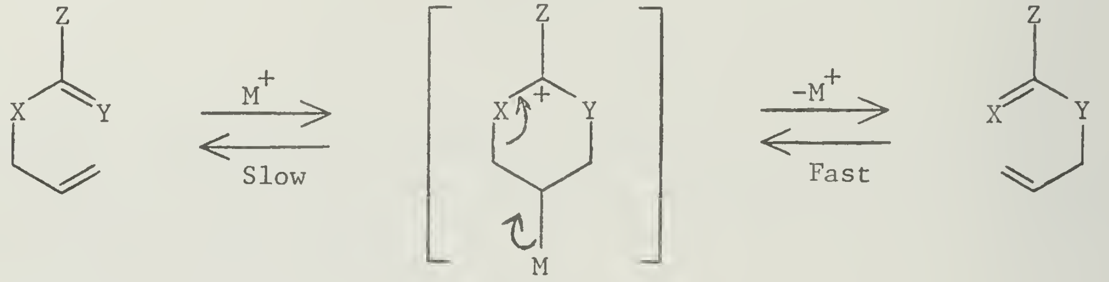
TRANSITION METAL CATALYSIS OF [3,3]-SIGMATROPIC REARRANGEMENTS

Reported by Sharbil J. Firsan March 5, 1981

[3,3]-Sigmatropic rearrangements have been extensively studied and widely used in organic synthesis.[1] However, structural features make it often desirable to carry out these transformations under milder conditions than those generally needed for the thermal process. Catalysis by transition metals of what amounts to an overall [3,3]-sigmatropic shift promises to be one way to achieve this goal.[2]

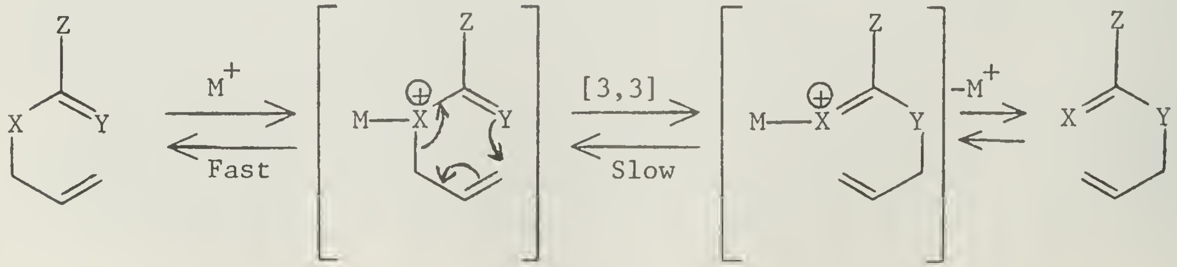
The interaction of a transition metal with a Cope or a hetero-Cope system can take one of three forms. In the first, the catalyst coordinates preferentially to the less hindered carbon-carbon π-bond to induce the formation of a 6-membered ring cationic intermediate. Fragmentation of this intermediate gives either the rearranged product or the starting material (Eq. 1). This "cyclization-induced"[3,4a] rearrangement mechanism is thought to be favored mainly by transition metals that are "soft" Lewis acids.[3,5,6] Reactions believed to proceed by such a mechanism include: (1) equilibration of allylic esters with $LiPd_2Cl_6$[4a] or $Pd(CH_3CN)_2Cl_2$,[6,7] (2) equilibration of allylic carbamates[3] and conversion of allylic trichloroacetimidates to trichloroacetamides[8] both promoted by $Hg(OOCCF_3)_2$, and (3) $Pd(PhCN)_2Cl_2$-catalysis of the rearrangement of cyclic[9,10,11] and acyclic[12] 1,5-dienes, and of the conversion of S-allylthioimidates to N-allylthioamides.[13] The Na_2PtCl_4-catalyzed rearrangement of 2-allyloxypyridine to 1-allyl-2-pyridone[14] probably proceeds by a similar mechanism.



(1)

X=C,O,S; Y=C,O,S,NR; Z=R,RO,CX_3,NR_2

Alternatively, the catalyst may coordinate to the heteroatom, thus acting like a "hard" Lewis acid[5] and giving rise to a concerted, "thermal type"[15] rearrangement mechanism (Eq. 2). This resembles very closely



(2)

catalysis by non-transition metal electrophilic reagents.[5,14,16-19] Thus $TiCl_4$ effectively catalyzes the rearrangement of *N*-allylenamines to α-alkylated aldehydes,[20a] and of allylaryl ethers to o-allylphenols.[20b] Allylphenyl ethers,[21] and *N*-allylanilines[22] are similarly rearranged through catalysis with $ZnCl_2$. Propargylphenyl ethers are converted to 2H-chromenes with $AgBF_4$,[5,23] and *N*-propargyl anilines to 1,2-dihydroquinolines with CuCl.[24]

Finally, a transition metal may induce a [1,3]-hydrogen or a [1,3]-alkyl migration in a system capable of undergoing a [3,3]-sigmatropic shift. Thus a [1,3]-alkyl shift is involved in the $Pd(PhCN)_2Cl_2$-promoted conversion of 4-vinylcyclohexene into 1,5-cyclooctadiene[25] and in the $Pd(P\phi_3)_4$ or $Pd(\phi_2PCH_2CH_2P\phi_2)_2$-catalyzed conversion of alkylidenetetrahydrofurans into cyclopentanone derivatives.[26] Similarly, a [1,3]-hydrogen migration isomerizes the allylic double bond of allylaryl ethers under the influence of $Pd(PhCN)_2Cl_2$[27a] or $RhCl_3$,[27b] and that of diallyl ethers under catalysis by $Ru(P\phi_3)_2Cl_2$[28] or $Fe_2(CO)_9$-morpholine.[29]

In an interesting synthetic application of transition metal catalysis of [3,3]-sigmatropic rearrangements, allylic acetate equilibration forms a key step in the synthesis of prostaglandins.[7,30]

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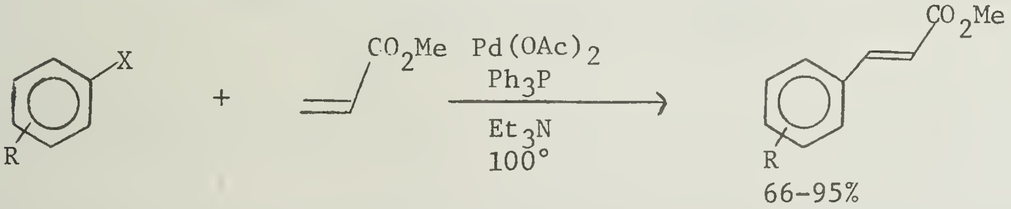
Heterocyclic Synthesis via Organopalladium Complexes

Reported by Thomas M. Stevenson   March 12, 1981

The discovery of the Wacker process[1] for the conversion of ethylene to acetaldehyde almost twenty years ago spurred interest in organopalladium complexes.[2] During the past decade these complexes have found increasing utility for the synthesis of natural products.[3] Palladium complexes have been shown to catalyze a large number of transformations which have little analogy in classical organic synthesis.[2] Among these is the propensity of palladium to facilitate the formation of carbon-carbon bonds as well as carbon-heteroatom bonds. This dual nature makes palladium especially suited for the synthesis of heterocycles.

The Heck Arylation Reaction. Of the reactions which have been adapted to heterocyclic synthesis, one of the most famous is Heck arylation or the vinylic substitution reaction.[4] In this process an organic halide is coupled with an olefin or acetylene. This reaction is quite general and shows that palladium complexes tolerate a wide range of functionality. (Eq. 1)



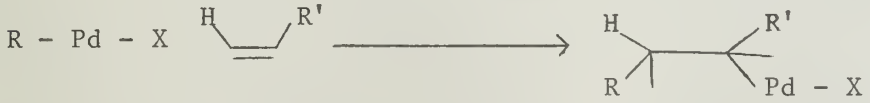
(1)

R = 4-Cl, 4-CN, 4-OCH$_3$ 3-OCH$_3$, 4-NO$_2$, 4-NH$_2$, 4-SCH$_3$, 4-NHAc, 2-CO$_2$CH$_3$, 2,5 di-iPr,

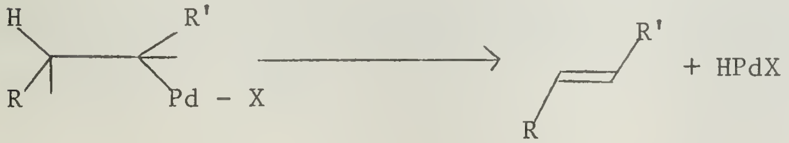
X = Br, I, Hg-Cl, Tl(OAc)$_2$

The proposed mechanism of the Heck arylation reaction points out the differing reactivities of palladium (0) and palladium (II) species.[5] Typical of palladium (0) is the oxidation addition reaction with organic halides (Eq. 2). The palladium (II) complex thus generated can react in a number of ways including addition to olefins (Eq. 3). These compounds readily undergo reductive elimination producing a hydridopalladium (II) complex while reforming the unsaturation usually in the E configuration (Eq. 4). This hydridopalladium complex is unstable to base and regenerates palladium (0) for another catalytic cycle (Eq. 5).

$$R - X + Pd^\circ \longrightarrow R - Pd - X \qquad (2)$$



(3)

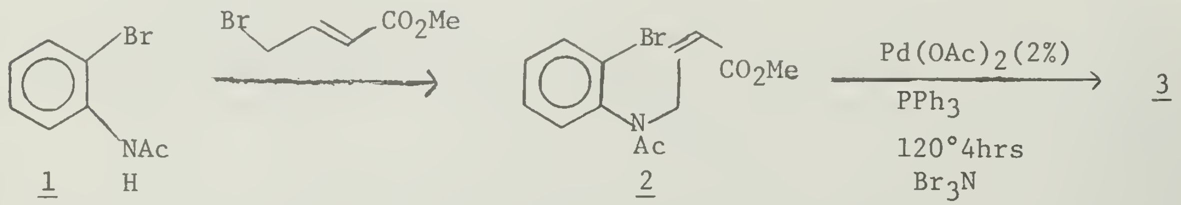


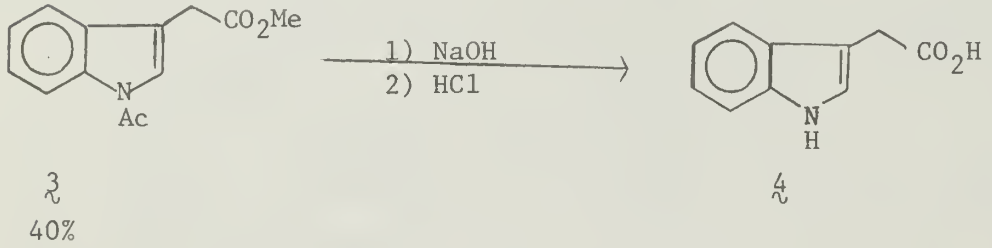
(4)

$$H - Pd - X + R''_3N \longrightarrow Pd^\circ + R''_3N^{\oplus}HX^{\ominus} \qquad (5)$$

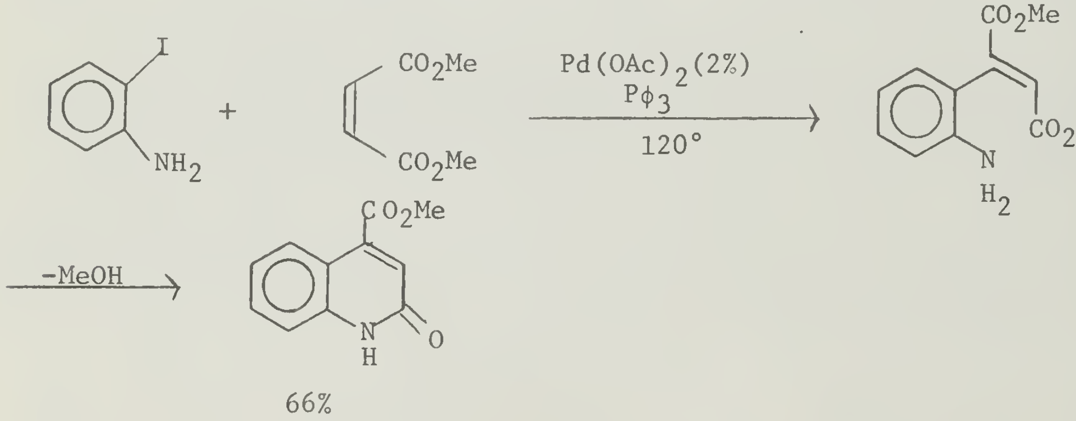
$Pd^\circ = PdL_4$ $L = PR_3, AsR_3$
$Pd = PdL_2$ $L = PR_3, AsR_3$

The first adaptation of this reaction to the synthesis of heterocycles was made by Ban in 1977.[6] He discovered that allylation of o-haloanilines provides substrates for vinylic substitution resulting in ring closure An example of this process is the synthesis of indoleacetic acid 4 from N-acetyl-O-bromoaniline 1. Allylation followed by cyclization with $Pd(OAc)_2$ and subsequent saponification results in the desired product.



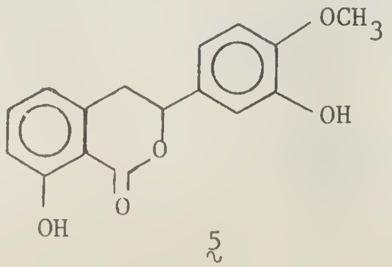


Heck has also adapted his own reaction to the synthesis of quinolones.[8] Use of substituted olefins such as dimethylmaleate in conjunction with o-iodoaniline leads to intermediates which can lose methanol to form cyclized products (Eq. 6) 4-substituted quinolones have been produced in 20-70% yields.



(6)

The Heck arylation reaction has been utilized in several natural product syntheses.[9,10] Recently a one step synthesis of analogues of the dihydroisocoumarin phyllodulcin 5 has been reported.[10] Condensation of a o-chloro mercurio benzoic acids 6 and 3,4-disubstituted styrenes 7 with lithium chloropalladite resulted in direct synthesis of the phyllodulcin skeleton 8



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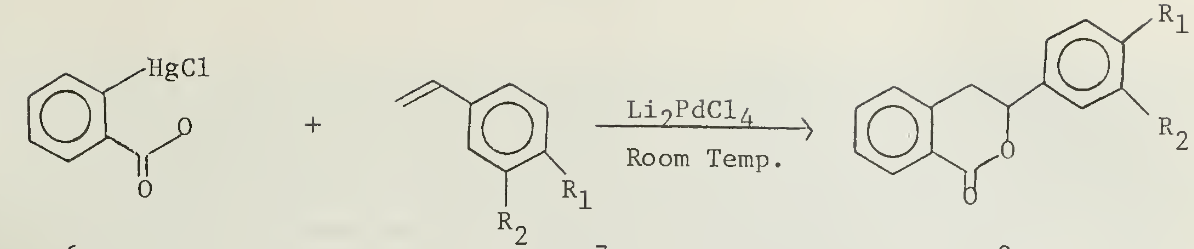
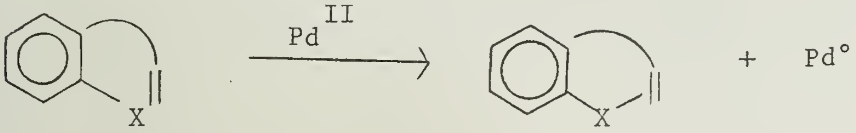


6 7 8

60%

R_1 = H, OCH_3, OAc
R_2 = H, OCH_3, OAc

Nucleophilic cyclizations. Palladium complexes can often react with nucleophiles.[11] This has formed the basis for a large number of heterocyclic syntheses of mono and bicyclic systems.[12-20] The general approach consists of an intramolecular reaction of a palladium (II) complex generated from an olefin with an internal nucleophile. (Eq. 7)



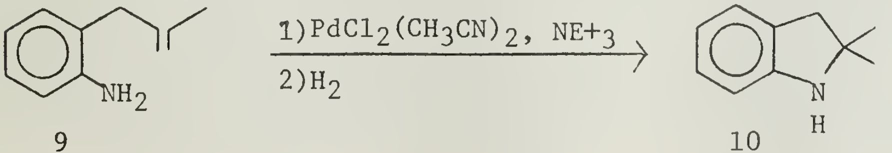
(7)

X = NH_2, OH, CO_2H

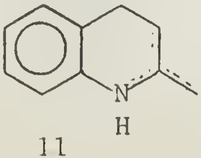
The formation of palladium (0) as a byproduct limits these procedures by necessitating the use of stoichiometric quantities of palladium. The addition of an oxidant such as benzoquinone or $CuCl_2$ sometimes solves this problem and allows catalytic conversion.

Hosokawa has synthesized a number of benzofurans from 2-allylphenols which are available from Claisen rearrangements.[12] O-Hydroxychalcones have been similarly cyclized to flavones.[13] Isocoumarins are available from o-allylbenzoic acids.[14] Hegedus has shown that quinolines and indoles may be obtained from o-haloanilines through the use of π-allynickel complexes followed by cyclization with $PdCl_2(CH_3CN)_2$.[15]

In some instances substrates may cyclize to either a five or six membered ring. This question of ring size preference has been studied by both Hosokawa[12b] and Hegedus.[15] Though the six membered ring is more readily formed, the main factor governing ring size is steric in nature. Cyclization occurs from the intermediate in which palladium occupies the least hindered position. This is exemplified by the exclusive formation of 2,2-dimethylindoline 10 from the methallylaniline 9. No trace of quinoline 11 was detected.[15]

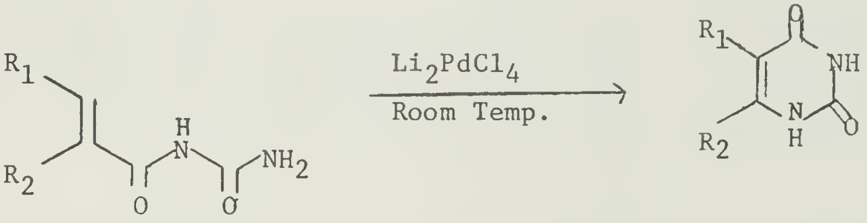


9 10



11

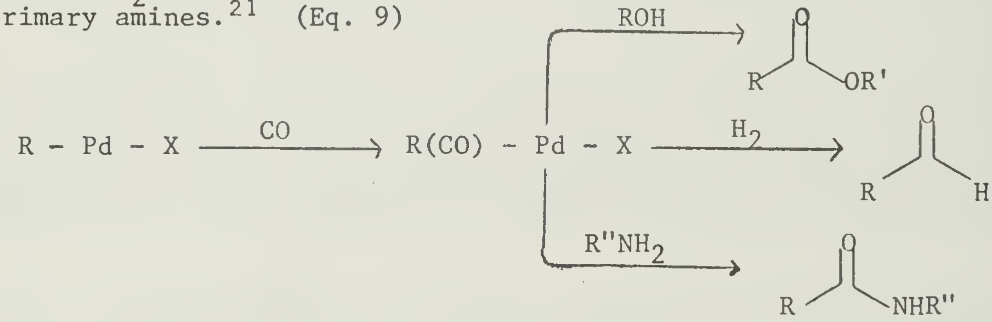
Monocyclic heterocycles have been synthesized by the palladium (II) mediated cyclization of of α-β unsaturated acid derivatives.[16-19] α-β unsaturated hydroxamic acids were cyclized to 3 isoxazolanes with a stoichrometric quantity of lithium chloropalladite.[16] Similarily, hydrazides may be converted to pyrazalones,[17] 2-pyridones can also be synthesized by this method.[18] Perhaps the most interesting and useful conversion affords uracil, thymine, and related pyrimidines.[19] Substituted unsaturated ureas may be cyclized to the desired products in fair to good yields. (Eq. 8) Unfortunately the feasibility of catalytic conversion has yet to have been investigated.



(8)

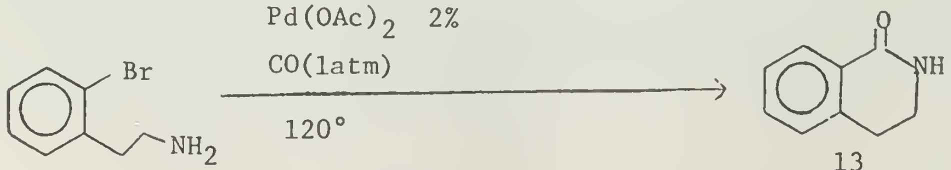
R_1 = H, Me, Et
R_2 = H, Me, Et

Carbonylation with Carbon Monoxide. At present the most active area of research in progress is the use of carbon monoxide insertion reactions. Interest in these reactions stems from the fact that palladium complexes derived from both olefins and organic halides can be carbonylated with carbon monoxide readily at room temperature and below.[20] Such carbonylated complexes can be reduced by H_2 to the aldehyde, esterified by alcohols, and converted to amides by primary amines.[21] (Eq. 9)



(9)

Ban and others have found that these reactions can occur by internal pathways.[22-36] If a nucleophile is located ortho to a halogen, cyclization can occur. Thus the reaction of o-bromophenylethyl amine 12 with $Pd(OAc)_2$ and carbon monoxide affords the desired isoquinolone 13 in 40% yield.[22]

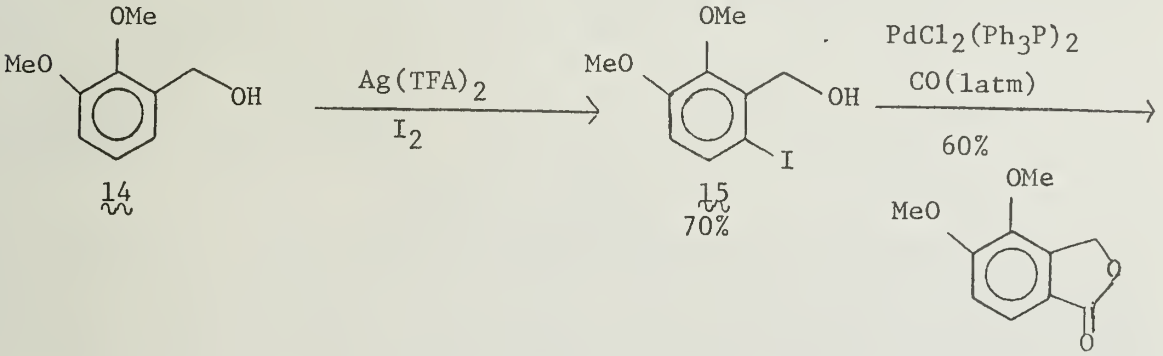


12

13

In the same way the five and seven membered benzolactams have been formed. A logical extension of this method is the synthesis of benzolactones and phthalides.[23] Cyclization of o-bromo-ω hydroxyalkylbenzenes leads directly to the desired lactones. In addition N-methylphthalimide has been synthesized in 85% yield from o-bromo-N-methylbenzamide.[24] Ban has also utilized his technology in an improved synthesis of the isoquinoline alkaloid sendaverine.[25]

The scheme leading to phthalides and lactones has been greatly improved and expanded by Stille[26] and Larock.[27] Stille has found that the high reaction temperatures previously employed are unnecessary and that oxidative addition employing a 0.5-3% $PdCl_2(PPh_3)_2$ catalyst system can take place at 50-60° aryl halides, 30°C for vinylic halides, and at room temperature or below for benzylic and allylic halides. These reactions can be carried out at lower temperatures with fewer side reactions and therefore with higher yield. Thus o-iodobenzyl alcohol can be converted to phthalide in quantitative yield at 55°C. The valuable psuedomeconin 16, previously difficulty accessible, can be easily synthesized from 2,3-dimethoxybenzyl alcohol 14. The phthalide is obtained by iodination followed by carbonylation at 55°.



14

15
70%

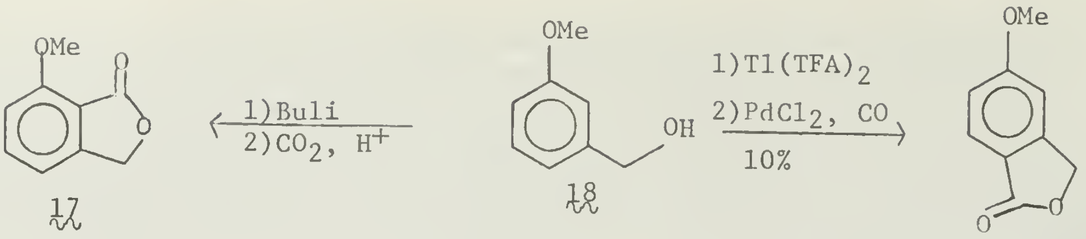
16
80%

Larock[27] has utilized the ability of palladium to undergo exchange or transmetallate with other organometallic complexes (Eq. 11).

$$R - M - X_n \xrightarrow{PdX_2} R - PdX + MX_{n+1} \tag{11}$$

M = Hg, Tl
X = halogen, trifluoroacetate

The work of Taylor and McKillop[28,29] has shown that thallation of benzyl alcohols, benzoic acids, esters, and amides occurs almost exclusively in the ortho position. Thus the use of thallium in concert with $PdCl_2$ and CO obviates the need to use organic halides as starting materials and expands the usefulness of these procedures accordingly. The thallation-carbonylation procedure nicely complements the well known directed metallation synthesis of phthalides.[30] When m-methoxybenzyl alcohol 18 is metallated with Buli and CO_2 is added the product is 7-methoxyphthalide 17. On the other hand where the same molecule is subjected to thallation-carbonylation only 5-methoxyphthalide 19 is produced.

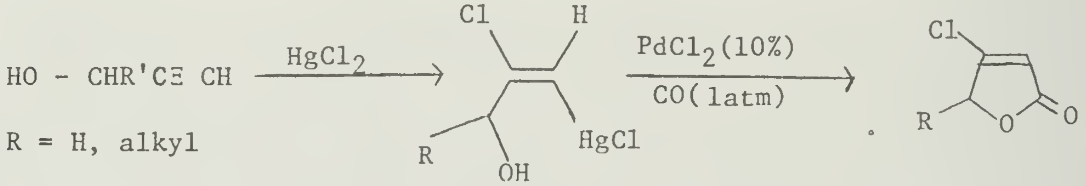


17 18 19

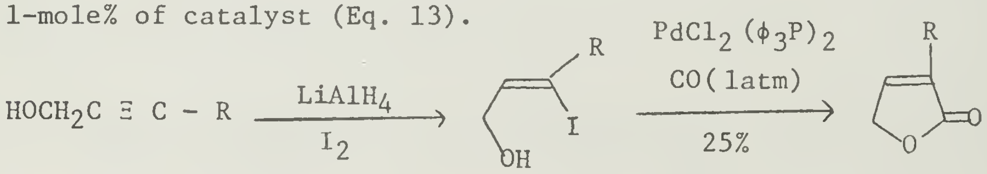
90%

Thallation-carbonylation has proved to be stereospecific as well. The use of either cis or trans 2-phenylcyclohexanol leads to tricyclic lactones in which the original configuration remains intact.

Transmetallation can also be useful for the synthesis of α-β unsaturated butenolides[31-33], a class of naturally occurring five membered lactones which serve a host of biological uses. Larock[31] has shown that mercuration of propargylic alcohols with $HgCl_2$ results in vinyl mercurials in which the necessary cis configuration for lactonization is inherent. Transmetallation with $PdCl_2$ proceeds with regiochemical integrity and subsequent carbonylation affords 3-chlorobutenolides which may be alkylated by Gilman reagents.[32,33] (Eq. 12)



Stille has reported this same overall conversion by a different method. He has used Corey's method for reduction of propargylic alcohols with I_2-$LiAlHy$[34] to synthesize iodoalkenes which can be easily carbonylated with $PdCl_2(Ph_3P)_2$ and CO.[35] The conversion proceeds in good to excellent yields often with less than 1-mole% of catalyst (Eq. 13).



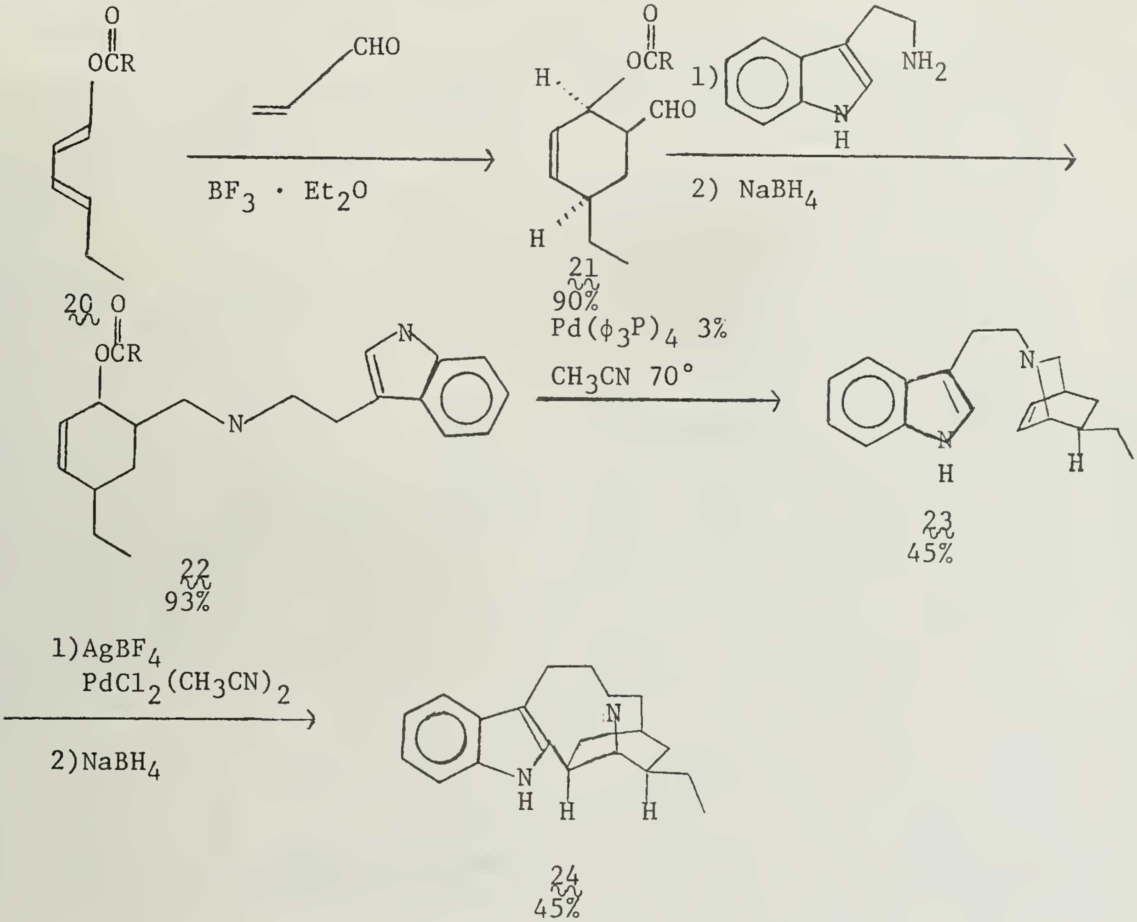
(13)

R = alkyl

Lactones have been synthesized directly from propargylic alcohols in a somewhat less favorable manner with $SnCl_2$/$PdCl_2$ catalyst system.[36] A forerunner of that reaction was utilized in the synthesis of an intermediate lactone in the synthesis of vernolepin.[37]

π-allyl complexes. The reaction of allylic acetates with palladium (0) results in the formation of π-allyl palladium complexes.[3] Trost has found that if these complexes are generated in the presence of an internal nucleophile intramolecular cyclization occurs.[38a] This methodology has been utilized for the synthesis of the iboga alkaloids.[38-39] Trost's recent synthesis of ibogamine[38b] in optically active form constitutes one of the most elegant uses of palladium in organic chemistry. The assymetric Diels-Alder reaction of acrolein and the 1,3-hexadiene-mandelic ester 20 results in the optically active aldehyde 21. Rx of the aldehyde with tryptamine followed by reduction results in 22, the key intermediate for cyclization. This cyclization is mediated by 3%

$Pd(PPh_3)_4$. Double bond isomerization is catalyzed by $AgBF_4$ and $PdCl_2(CH_3CN)_2$ resulting in an 80-20 mixture of enantiomers. The chirality was induced by the use of the o-methylmandelyl group.



Synthetic approaches such as Trost's show the immense utility that palladium can display. Though palladium is expensive the number of time saving transformations it can catalyze make further investigations into the synthesis of other heterocyclic natural products inevitable.

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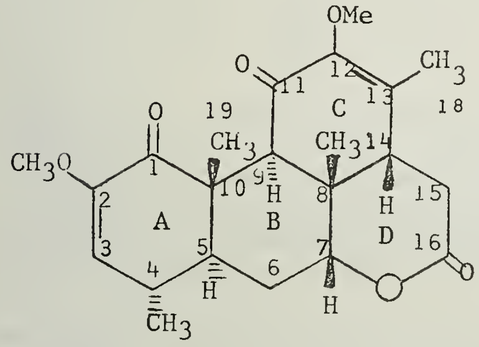
SYNTHETIC APPROACHES TO QUASSINOIDS

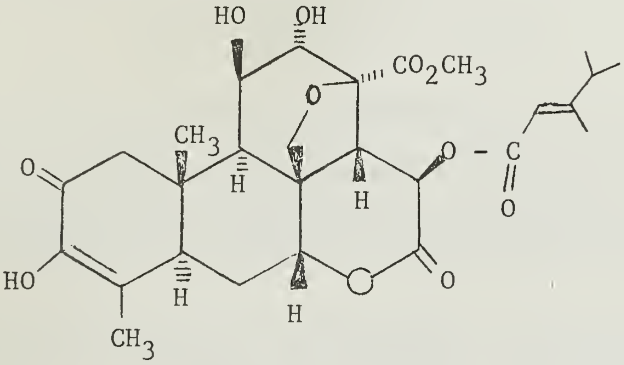
Reported by Dale O. Kiesewetter March 23, 1981

Quassinoids, tetracyclic diterpenes isolated from plants of the Simarubacea family, possess 5 to 7 adjacent chiral centers and a high degree of oxygen functionality as indicated by the representative structures depicted in figure I.

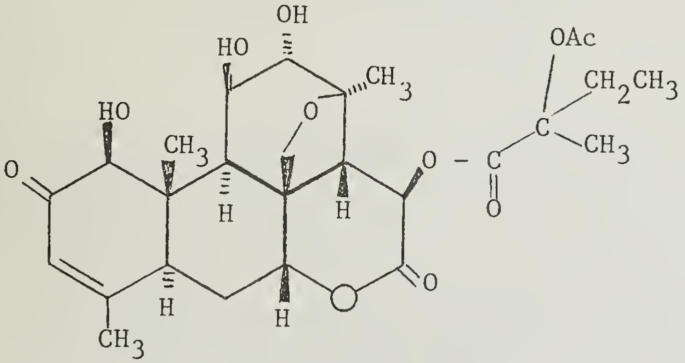
Figure I



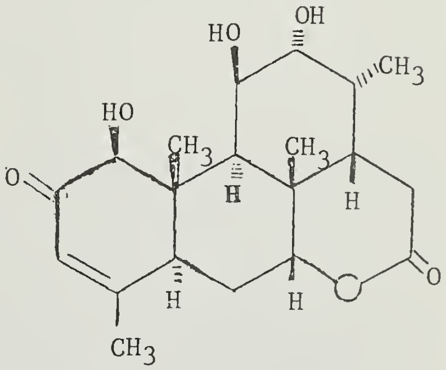
(1) Quassin



(2) Bruceantin



(3) Quassimarin



(4) Klaineanone

Quassin (1) and neoquassin, the corresponding lactol, were first isolated as the bitter principles of extracts of Quassia amara by Winckler in 1835.[1] After years of acquisition of physical and chemical data by many workers,[2,3a] the structures and stereochemistry of quassin and neoquassin were deduced by Valenta in the early 1960's with the aid of the then new technique of nuclear magnetic resonance.[3] Since Valenta's work, many quassinoids have been isolated and assigned structures. A thorough review of quassinoids was published by Polonsky in 1973.[4]

Biogenetic studies indicate that the quassinoids are derived from acetate via a triterpene intermediate in a manner similar to the steroids[4]; one of the general synthetic approaches is based on degradation of steroidal precursors.

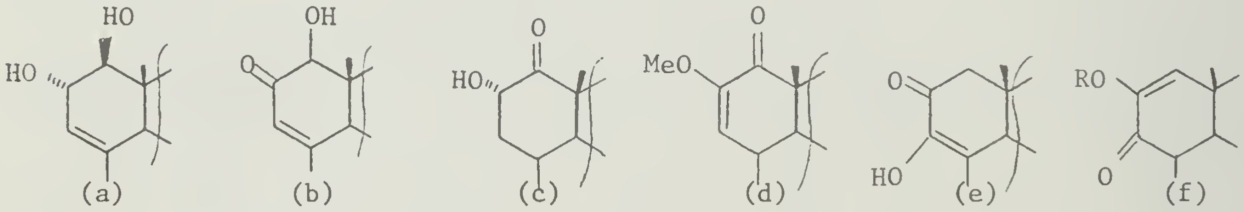
Beginning in 1975, reports emerged of synthetic approaches to these molecules. A brief discussion of the interest created by the biological activities of some of the quassinoids will be followed by a presentation and discussion of the synthetic approaches.

Biological properties. The discovery of antitumor activities inherent in some of the quassinoids has heightened interest in devising efficient synthetic approaches to these compounds. Bruceantin (2), isolated by Kupchan in 1975 from *Brucea antidysenterica*, is a potent antitumor agent.[5] *In vitro* activity has been displayed against cultured human carcinoma of the nasopharnyx (KB system) and P388 mouse leukemia.[5] Extracts of this plant had been used to treat cancer prior to the isolation of bruceantin.[6] Other quassinoids also show antitumor properties.[7]

Surveys of structural requirements for biological activity have resulted in defining essential and highly desirable features. The $\Delta^{3,4}$-2-oxy moiety in the A-ring, ester functions at C-6 and/or C-15, and the lactone moiety in ring D are essential for activity. The presence of an epoxymethano bridge between C-8 and C-11 or C-8 and C-13 is also considered essential for biological activity. Free hydroxyl groups at C-1 and C-12 are highly desirable.[7]

Structural Information. Several different A-ring functionalizations have been reported for members of this class of compounds.[4,7c] Figure II shows some of the more common structures.

Figure II



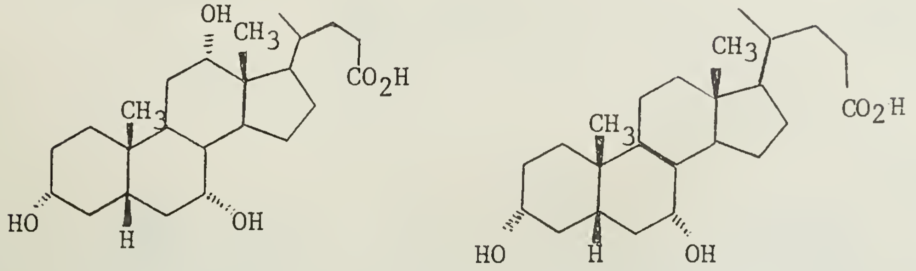
(a) (b) (c) (d) (e) (f)

The 8β substituent is either a methyl group or a hydroxymethyl group forming a hemiketal to C-11 or an oxide bridge to C-13.[4] The ring formed by this bridging is the E ring. Of the chiral centers present in quassin, four must be established early in the synthesis; the others are in the thermodynamically favored configuration.[3b,8]

Synthetic Approaches. Two general synthetic approaches to quassinoids have been reported. One strategy involves degradation of steroidal precursors. The presence of most of the proper chiral centers in the steroid skeleton precludes the need for resolution of enantiomeric mixtures.[9a] Three key transformations are involved in this approach: a) cleavage of the steroidal D-ring and conversion to a lactone; b) introduction of oxygen functionality in the A-ring; and c) introduction of the 8β substituent. The second approach utilizes the stereoselectivity of [4+2] cycloaddition or other potentially selective cyclization to generate the proper stereochemistry.

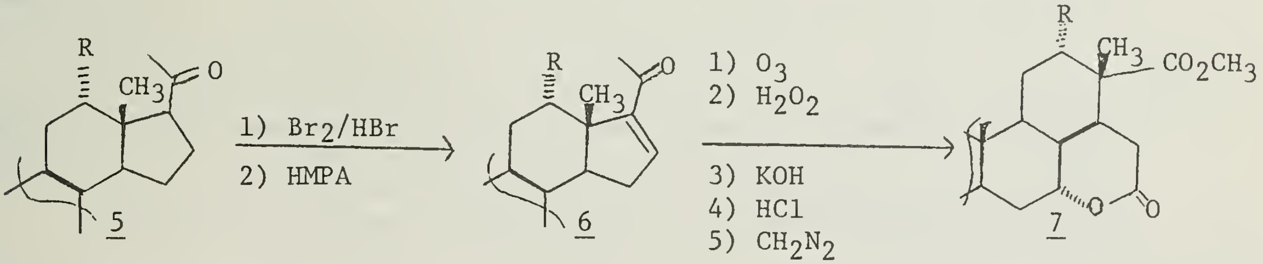
Degradative Approaches. Dias and co-workers[9] selected cholic acid and chenodeoxycholic acid (figure III) as starting material for their approach to quassin and quassin derivatives. They have devised methodology for the D-ring conversion[9] and have formed diosphenol A-rings.[9b]

Figure III

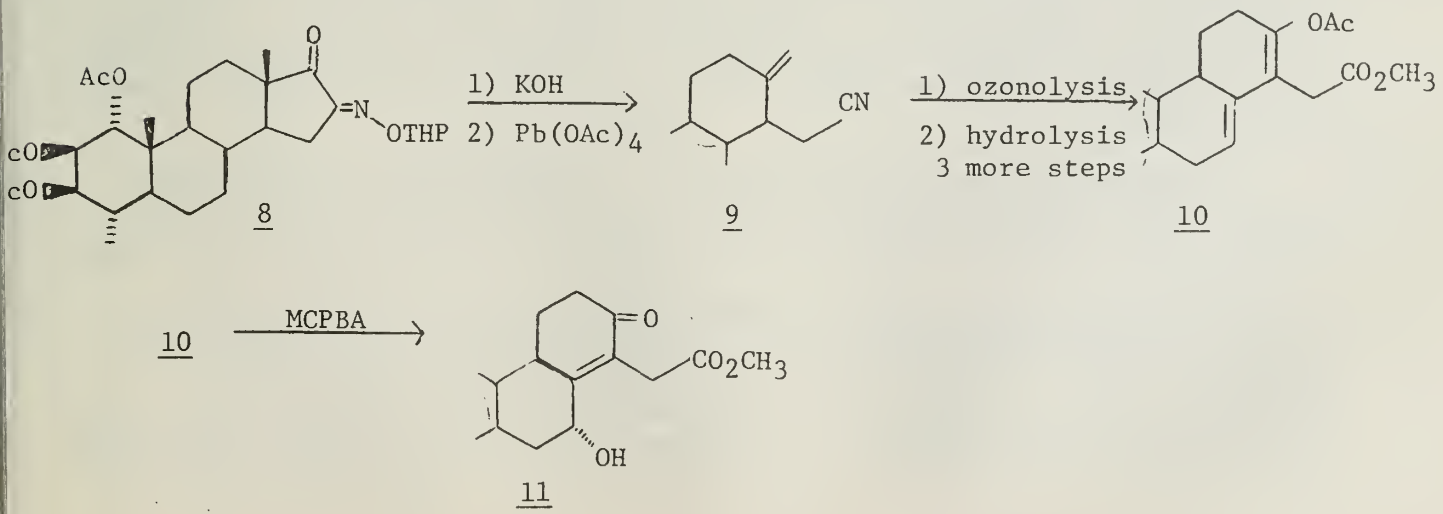


cholic acid chenodeoxycholic acid

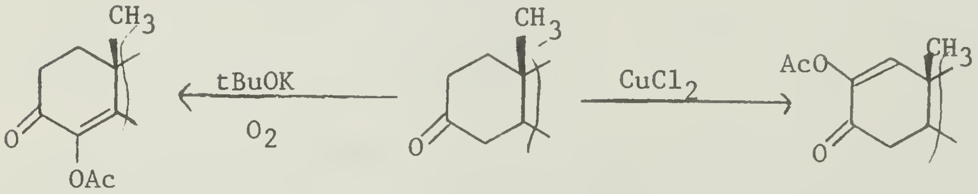
The ester of chenodeoxycholic acid was subjected to a modified Barbier-Wieland side chain degradation to form ketone 5. The enone 6 was generated and subjected to ozonolysis forming the diacid which was converted to the lactone 7.



Pfenninger and Graf[10] have degraded testosterone in their approach to quassin. Steroidal D-ring cleavage was effected by treating 16-oxime-O-tetrahydropyranyl ether-17-keto steroid, 8, with potassium hydroxide followed by oxidative decarboxylation, providing the desired exocyclic olefin, 9, in low yield. Other approaches to 9 have been examined.[10,11] Olefin 9 was ozonolyzed to the ketone and the nitrile converted to an ester; three additional steps led to the dienol acetate, 10. Oxidation of 10 with m-chloroperoxybenzoic acid afforded the 7α-hydroxy-$\Delta^{8,14}$-13-keto compound 11 which was easily converted to the lactone.



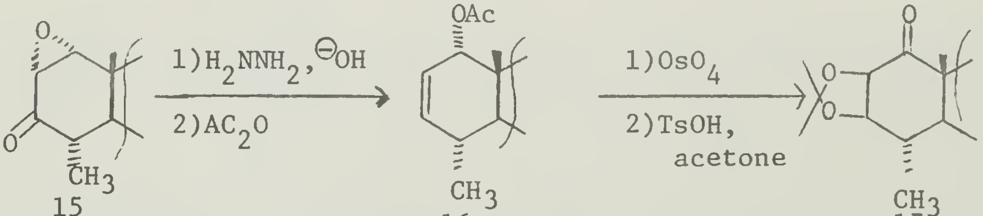
Dias has prepared two isomeric diosphenol acetates from the 3-keto steroid. Selectivity was possible by choice of reagents. Treatment of the 3-keto steroid 12 with potassium t-butoxide under oxygen, followed by acetylation, led to the $\Delta^{4,5}$-diosphenol acetate 13 in up to 43 percent yield. Minor products of this reaction were not characterized. Alternatively, treatment with $CuCl_2$ in aqueous acetic acid, followed by acetylation, led predominantly to the $\Delta^{1,2}$-diosphenol acetate 14 (35%) along with 13 (10%).



13 12 14

Dias has yet to combine the formation of the A-ring diosphenol with the formation of the lactone in the same synthetic scheme. Further study of the proper sequencing of steps and utilization of protecting groups is necessary.

Pfenninger and Graf[10] converted the enone of testosterone into the A-ring of quassin via a long sequence which required manipulation of protecting groups. The 4α-methyl group was introduced by reductive alkylation of the enone with methyl iodide in lithium/NH_3. Generation of the $\Delta^{1,2}$ enone followed by epoxidation with basic hydrogen peroxide yielded 15.

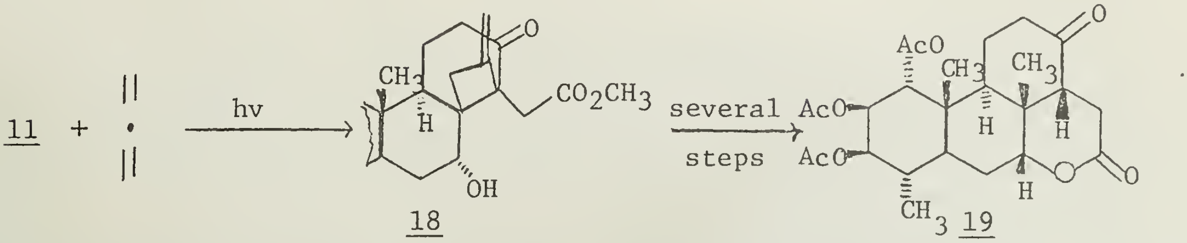


15 16 17

The key 1,3 carbonyl transposition was effected by subjecting 15 to the Wharton reaction and subsequent acetylation to attain the $\Delta^{2,3}$ allyl acetate, 16. Hydroxylation of the olefin with catalytic osmium tetroxide, protection of the syn diol, hydrolysis of the acetate, and oxidation completed the 1,3 carbonyl transposition yielding 17. 17 was easily converted to the quassin A-ring.

Proper sequencing and suitable use of the protecting groups have been used to prepare both an A-ring intermediate and the D-ring lactone on the same molecule. The 8β methyl group has also been introduced into this system.

The introduction of the 8β methyl group began with a photochemical [2+2] cycloaddition between allene and 11 which provides regio- and stereospecifically 18.[10b] The observed regio- and stereoselectivity of this reaction is well precedented.[12] Ozonolysis of the exocyclic olefin provided a 1,3 diketone which undergoes cyclobutane ring opening to an 8β acetic acid. The acid was converted to the selenoester which was cleaved with tributyltin hydride[13] to provide 19 in low yield. 19 was the final intermediate reported by Pfenninger and Graf. Completion of the A-ring transformation has not been reported but should occur smoothly. Introduction of the C-ring functionality is still unformulated.

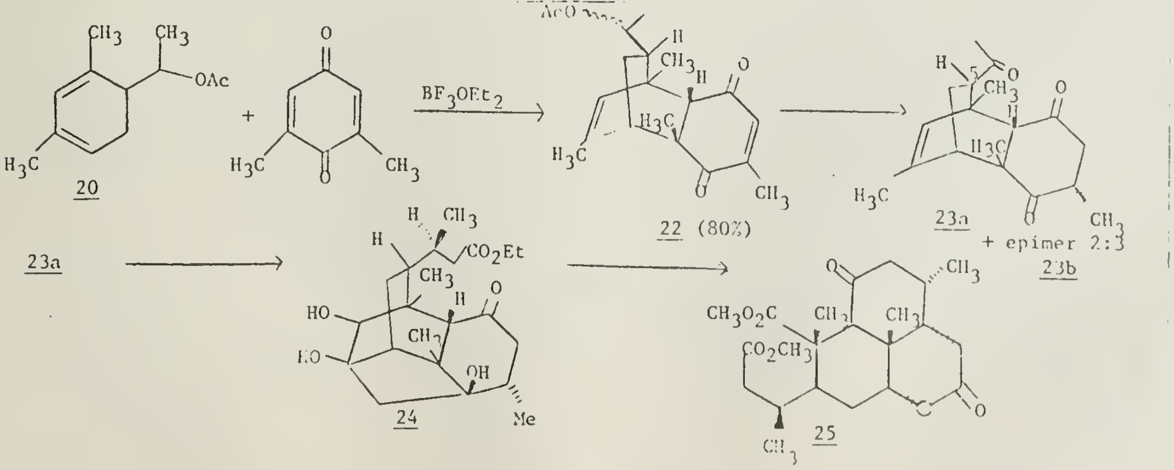


From these degradative studies, one can conclude that a 3-keto function will provide access to diosphenols in the A-ring. Methods for 1,2 carbonyl transpositions necessary for formation of the highly desired 2-keto diosphenols are known.[14] Long and tedious synthetic transformations involving manipulation of protecting groups are required to achieve the desired molecules. Although the introduction of the 8β methyl to 11 is quite elegant, perhaps hydrocyanation or cuprate addition to an appropriate enone would provide the same product.

Synthetic approaches using [4+2] cycloadditions. Use of the [4+2] cycloaddition reaction to form the B- or C-ring enables the desired configuration to be established at four centers. Four synthetic approaches using this cycloaddition as the key step have been published.

Valenta and co-workers[15] have prepared a racemic A-ring seco intermediate in the total synthesis of quassin. Their approach, summarized in figure IV, utilized a [4+2] cycloaddition between cyclic diene 20 and quinone 21. With one equivalent of boron trifluoride etherate, reversal of the normal regioselectivity was observed, which provided a desired substitution pattern. The quinone became the C-ring of the skeleton and the ring formed in the reaction became the B-ring of the skeleton. Further synthetic transformations resulted in formation of the lactone D-ring and homologation to the seco A-ring. The intermediate had the proper configuration at all carbons except C-4; facile epimerization of this center is predicted following ring closure.[3]

Figure IV

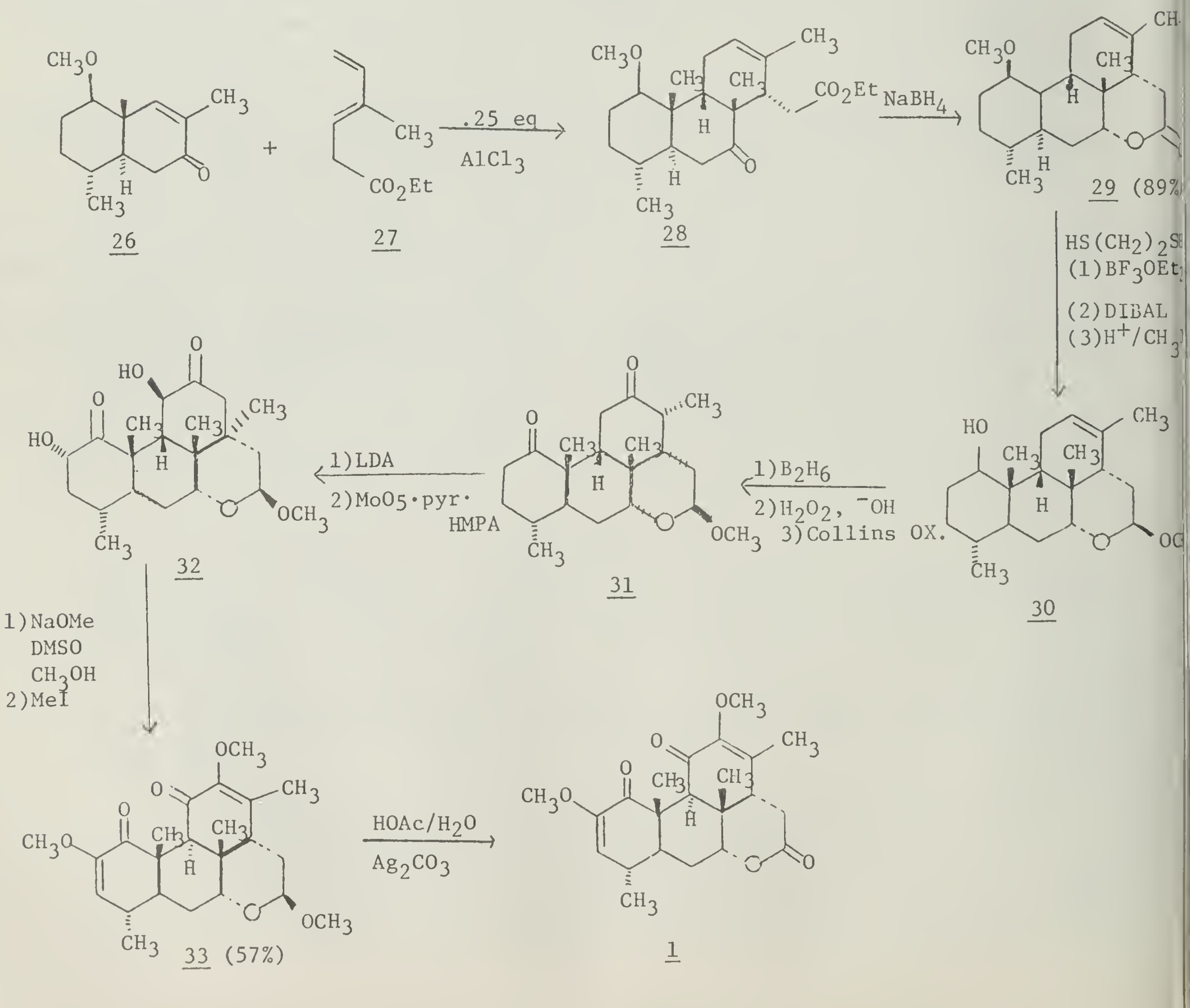


One of the stumbling blocks of this sequence is the epimerization at C-5 of 22 to the desired configuration. In his early work,[15a] Valenta reported a longer sequence that results in quantitative epimerization. Completion of the synthesis requires two major conversions; closure of the A-ring, possibly by an acyloin condensation, and introduction of an oxygen function at C-12.

Grieco's total synthesis of racemic quassin (figure V)[8,16] utilized a [4+2] cycloaddition of an appropriately substituted bicyclic enone 26 to the substituted diene 27 to yield the tricyclic intermediate 28. The yield of this step was low (40%) due to unfavorable steric interactions in the endo transition state. A recent report indicates that yields up to 65% have been achieved.[16b]

The conversion of 31 to 32 involved an interesting hydroxylation of an enolate using MoO_5/pyridine/HMPA according to the procedure of Vedejs.[17] Although diastereomers were produced, all were converted to 33 under the same conditions.

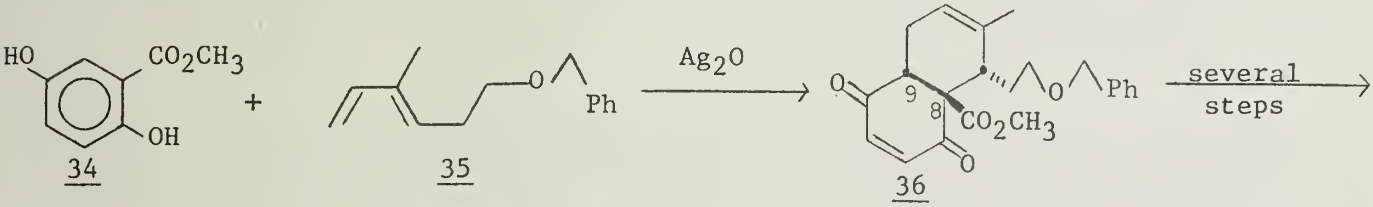
Figure V

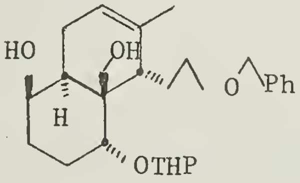


The most interesting conversion in this synthesis was the one pot conversion of 32 to 33. In this single laboratory manipulation, two centers are oxidized, two oxygens methylated and C-9 epimerized to yield a product easily converted to quassin. This step proceeded in 57% yield. The overall yield of this synthesis was 2.9% from 26.

Kraus and Taschner[18] have approached the synthesis of quassimarin by utilizing a [4+2] cycloaddition between a quinone generated in situ and a diene. These authors also developed the methodology of in situ oxidation of a hydroquinone to the corresponding quinone in the presence of dienes with silver oxide.[19] In contrast to Valenta's similar approach, the quinone moiety forms the B-ring of the backbone structure. Kraus and Taschner desired to form the tetrahydrofuran E-ring, which was not required in Valenta's target molecule. The C-ring of quassimarin does not require a diosphenol moiety; instead a trans diaxial diol is present at C-11, C-12.

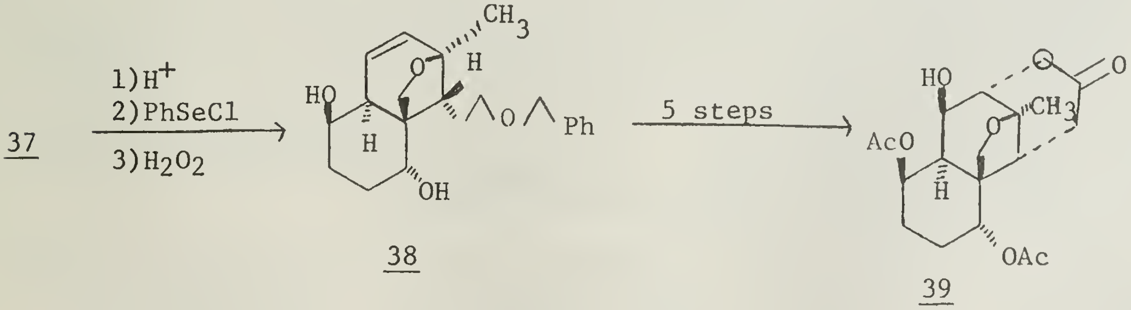
The cycloaddition between hydroquinone 34 and diene 35 in the presence of silver oxide proceeded in 95% yield to give adduct 36 having the 8β, 9β configuration. 36 was converted to 37 in several steps involving reductions and C-9 epimerization.





37

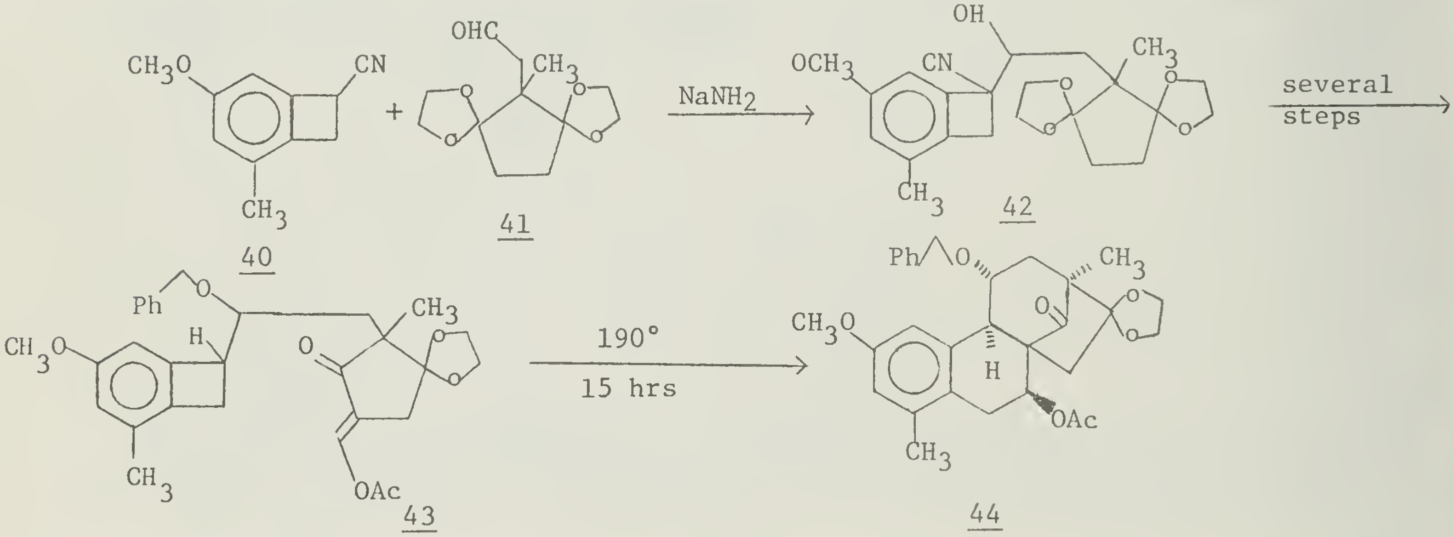
The E-ring was introduced by selenocyclization.[20] Cleavage of the THP ether followed by treatment with phenyl selenium chloride and oxidative workup converted 37 to 38.



Introduction of the trans diaxial diol was perceived as nucleophilic opening of an epoxide. This approach failed probably due to steric hindrance. This problem was circumvented using an approach which involved intramolecular epoxide opening in five steps from 38. The olefin was epoxidized and the alcohols protected as acetates. Deprotection of the benzylated alcohol followed by oxidation yielded an acid. Acid catalyzed intramolecular epoxide opening yielded 39.

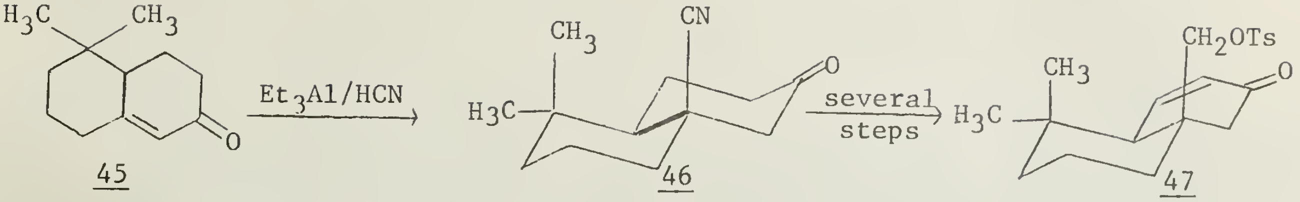
Formation of the lactone D-ring should be a matter of hydrolysis and relactonization. However introduction of the A-ring, which could conceivably involve an annulation, will require selective protection and deprotection steps. Introduction of the A-ring may be more feasible earlier in the synthesis.

Kametani and co-workers[21] have devised an approach using their famous thermal intramolecular [4+2] cycloaddition of benzocyclobutene derivatives. Both the B- and C-rings were formed with proper stereochemistry at the ring juncture during the course of the cyclization. Utilizing a convergent strategy, a substituted benzocyclobutene 40[22] was condensed with aldehyde 41.[23] Introduction of an exocyclic olefin onto the five-membered ring of 42 was accomplished via a series of steps to provide 43. The thermal cycloaddition proceeded in 41% yield giving adduct 44.

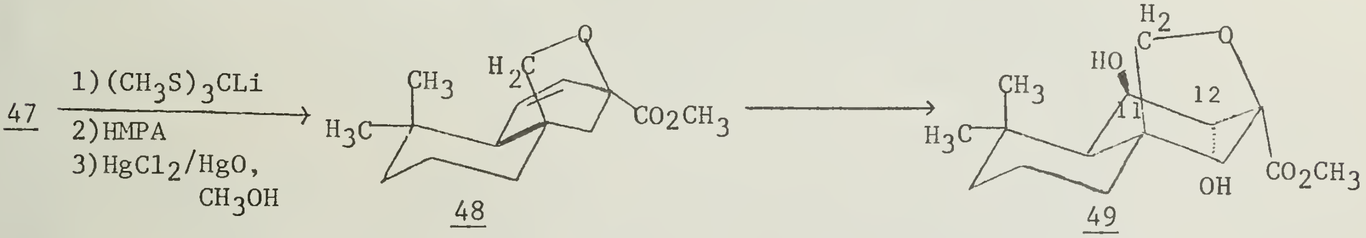


Kametani has proposed some of the remaining steps in the synthesis. The removal of the ketone at C-16 by the method of Marshall[24] followed by a two carbon homologation should provide access to the D-ring lactone. Birch reduction should provide a $\Delta^{1,10}$-2-enone which should provide access to the A-ring functionalization. Finally, the oxygen function at C-11 should provide access to C-ring functionalization.

Dailey and Fuchs[25] have synthesized a model of the BCE ring system of bruceantin without the use of cyclization reactions. Hydrocyanation of enone 45 with triethylaluminum-hydrogen cyanide led to isolation of 46 in 57% yield. Several steps were required to convert 46 into 47 including hydrolysis of the nitrile and introduction of unsaturation.



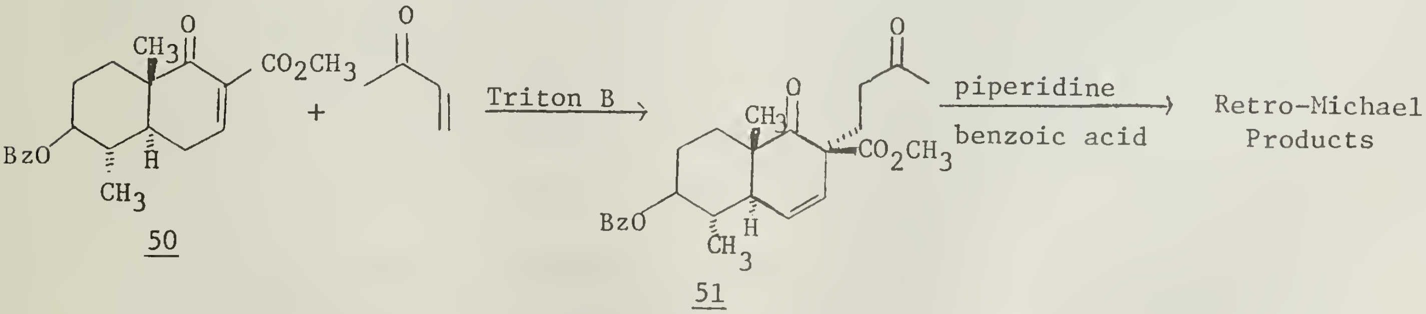
These authors reasoned that attack of cyanide on the carbonyl should cause intramolecular displacement of the tosylate by the intermediate cyanohydrin. This strategy worked in the model system lacking the unsaturation. With 47, however, the identified major product had a cyclopropyl ring at the ring juncture. The desired nucleophilic attack at the carbonyl was effected using the carboxylate anion synthon [tris(methylthio)methyl]lithium. Formation of the five-membered tetrahydrofuran ring was not spontaneous but required 24 hours of heating in HMPA at 90°C. Hydrolysis of the synthon and esterification yielded 48.



The trans diaxial diol was perceived as the product of epoxide ring opening. Both epoxides were formed, but hydrolysis led to complex mixtures lacking desired products. The desired trans diaxial diol was acquired by hydroxylation of olefin 48 with OsO_4 followed by DMSO-trifluoroacetic anhydride oxidation to the 12-hydroxy-11-keto compound. Reduction of the ketone from the less hindered face with sodium cyanoborohydride provided the desired diol 49.

If these procedures work with the more highly substituted substrates required for the real system, synthesis of bruceantin could be a reality in the near future. 45 needs to be elaborated to contain a ketone A-ring and an oxygen functionality at the center corresponding to C-7.

Watt and co-workers[26] attempted an approach to bruceantin utilizing a Robinson annulation to form the C-ring. The strategy involved Michael addition of the hindered ketone 50 to methyl vinyl ketone followed by aldol condensation to complete the annulation. Watt was unable to complete the hindered aldol condensation even utilizing previously successful methodology.[27]



In the short time that synthetic approaches have been reported, a great deal of progress in synthesizing certain partial structures has been made.

In spite of the fact that only quassin has been synthesized, methodology for preparing related structures is presently available. The most difficult problem is developing the strategy for employing compatible protecting groups to allow the desired transformations. Utilization of [4+2] cycloaddition reactions has provided the desired stereochemistry at most of the centers. Where improper stereochemistry has been generated by cycloaddition, the presence of oxygen functionality has allowed facile epimerization. With present methodology, the total synthesis of biologically active quassinoids and derivatives should be a reality within the next few years.

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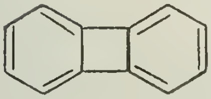
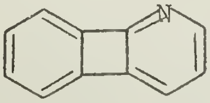
NONBENZENOID ANALOGUES OF BIPHENYLENE

Reported by Marc d'Alarcao March 26, 1981

Cyclobutadiene has been a compound of considerable theoretical interest to chemists for many years. Its study, however, has been hampered by its high reactivity[1], and this has led chemists to attempt the synthesis of cyclobutadienes with substituents which would impart stability to the basic ring system. Lothrop's successful synthesis[2] of the stable hydrocarbon biphenylene (I) in 1941 suggested that one solution to this problem is annelation of the cyclobutadiene ring with aromatic rings; since then numerous accounts of substituted biphenylenes have appeared in the literature.[1] This approach has been extended recently to include the introduction of nonbenzenoid aromatic substituents to the cyclobutadiene ring.


I



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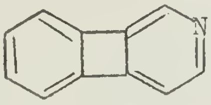

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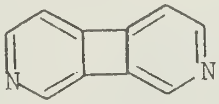

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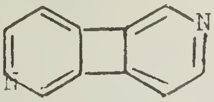
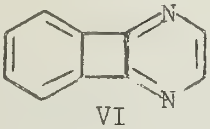


V



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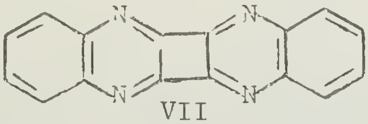
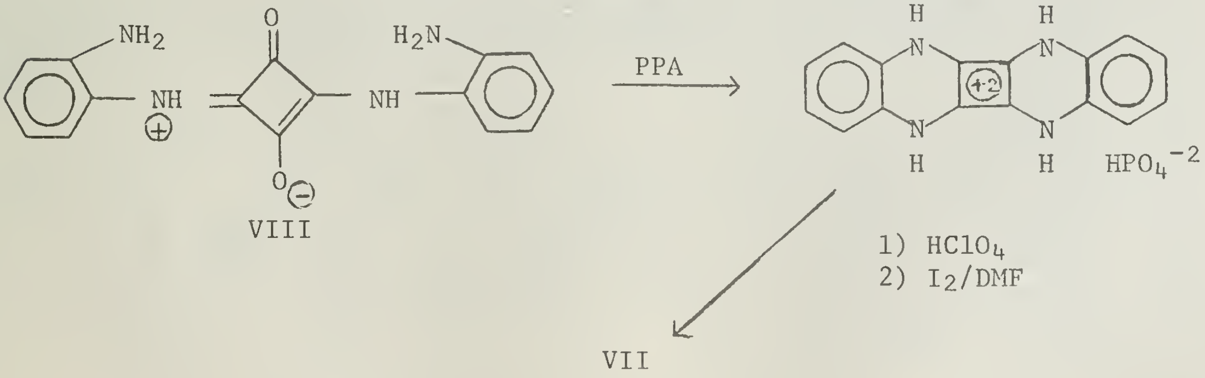


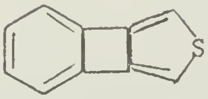
VII

A number of azabiphenylenes (II-VII) and their derivatives have been prepared in the last decade, by four distinct routes: a) reaction of photochemically or thermally derived 3,4-pyridyne to form head to head (IV) or head to tail (V) dimers[3], b) reaction of benzocyclobutenedione with o-phenylene diamines to form 1,4-diazabiphenylenes (VI)[4], c) thermal extrusion of nitrogen from aza-derivatives of benzo[c] cinnoline to give azabiphenylenes (II[5], III[5], IV[6], VI[7], VII[7]), and d) cyclization and oxidation of the squaric acid derivative VIII[8]. (Scheme I)

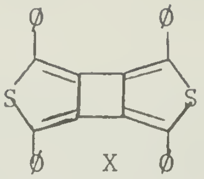
Scheme I



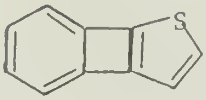
Three thiophene annellated analogues of biphenylene have been synthesized. Two of these (IX[9] and X[10]) are reasonably stable at room temperature and IX has been oxidized to the corresponding sulfone.[9] In contrast to this 1-thianorbiphenylene (XI) is quite unstable and forms [4+2]π dimers on standing under nitrogen.[11]



IX

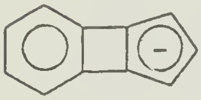


X

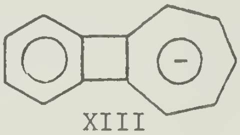


XI

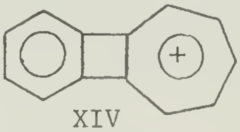
Certain carbocyclic nonbenzenoid derivatives of biphenylene have also been reported. The norbiphenylene anion (XII) has been observed in solution, despite its rapid dimerization[12], and NMR data has been recorded for the bridged [14] annulene XIII.[13] The tropylium cation derivative XIV has been isolated as its hexafluorophosphate salt[14] and is relatively stable at room temperature. Although XV has not as yet been prepared, a dibenzoannellated derivative of this anion has been reported.[15]



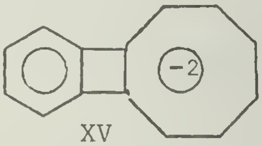
XII



XIII



XIV



XV

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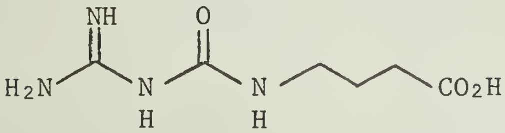
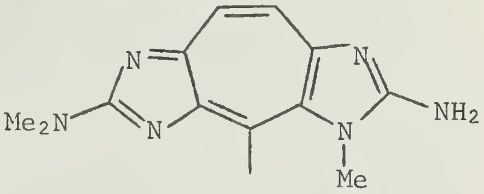
UNIQUE BIOACTIVE GUANIDINE-CONTAINING MARINE NATURAL PRODUCTS

Reported by Gary C. Harbour April 2, 1981

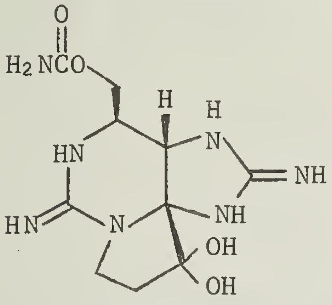
Marine organisms have been found to produce a wide variety of secondary metabolites containing the guanidine moiety.[1] These guanidine derivatives can be divided into four categories: 1) simple guanidino-acids (eg. 1), 2) pigments including bioluminescent compounds (eg. 2), 3) toxins (eg. 3a-b), and 4) bioactive compounds including antimicrobial agents, antitumor agents, and antiviral compounds (eg. 4-17). Today's seminar will examine the last category, the bioactive guanidine-containing marine natural products.



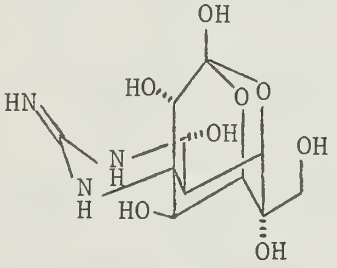
1 gongrine



2 zoanthoxanthin

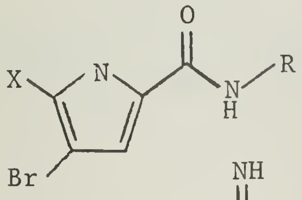


3a saxitoxin

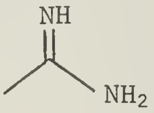


3b tetrodotoxin

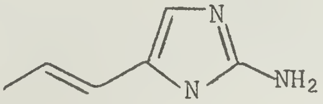
Many bioactive marine compounds have been found to contain guanidine groups. These compounds have been found to possess antimicrobial, antifungal, antitumor, and antiviral activities. These compounds can be placed into four structural groups: 1) pyrrole derivatives, 2) indole derivatives, 3) fatty acid amides of spermidine (or homospermidine) or its precursors, and 4) cyclic N,N'-disubstituted guanidines.

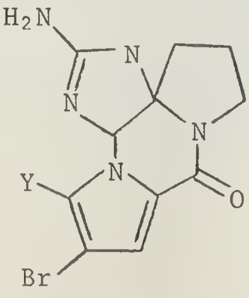


4 X=H R=



5 X=Br R=



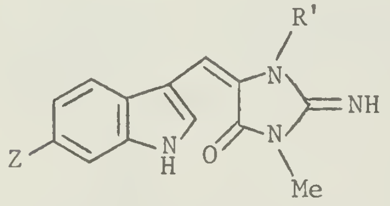


6 Y=Br

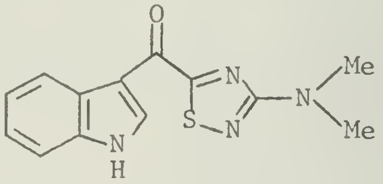
7 Y=H

The pyrrole derivatives include compounds 4-7.[2-5] 4-Bromopyrrole-2-(N'-amidino)carboxamide (4) is the simplest and first discovered of the pyrrole antibiotics.[2] It was isolated from the Caribbean sponge *Agelas*. Oroidin (5),[3,4] while in itself not a reported antibiotic is probably the biosynthetic precursor for the phakellin antibiotics [dibromophakellin (6) and 4-bromophakellin (7)].[5]

The indole derivatives (8-11)[6-9] are typified by aplysinopsin (8) isolated from an *Aplysinopsis* sp.[6] and *Verongia spengellii*.[7] These compounds all show cytotoxicity to cancer cell lines. Aplysinopsin, for example, shows ID_{50} values of 3.8, 0.87, and 3.7 μg/mL vs P388, KB, and L1210 cell lines, respectively. The most divergent of the series dendrodoine (11) isolated from a tunicate (*Dendrodoa grossularia*) was cytotoxic to L1210 cell lines.[9]

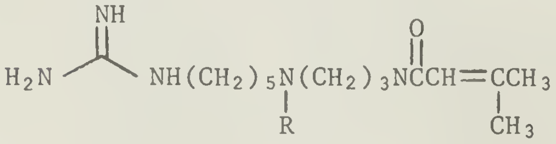


8 Z=H R'=Me
9 Z=H R'=H
10 Z=Br R'=H

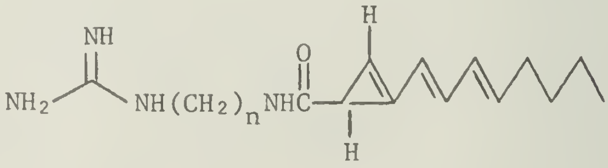


11

The acarnidines (12-14)[10] and the polyandrocarpidines (15 and 16),[11] are all amides of fatty acids. The acarnidines are based on a homospermidine backbone and differ in the length and degree of saturation in a fatty acid side chain. The polyandrocarpidines have identical fatty acid side chains but differ in the backbone being either agmatine or or homoagmatine. It is of interest that the acarnidines come from a sponge (*Acarnus erithacus*), while the polyandrocarpidines are isolated from a tunicate (*Polyandrocarpa* sp.). Both groups are antimicrobial and antiviral, while the polyandrocarpidines are also cytotoxic to L1210 (ID_{50} = 4.8 μg/mL) and KB cancer cell lines.



12 $R=-CO(CH_2)_{10}CH_3$
13 $R=-CO(CH_2)_3CH=CH(CH_3)_5CH_3$ (Z)
14 $R=-COC_{13}H_{21}$



15 n=5
16 n=4

Ptilocaulin and isoptilocaulin have been found in a variety of sponges including Ptilocaulis gracilis.[12,13] They are antibacterial and cytotoxic to L1210 cancer cells (ID_{50} = 0.39 μg/mL for isoptilocaulin).

Guanidine compounds have been found to be common among the bioactive marine natural products and no doubt many more will be found. Studies of these compounds may lead to the development of better antimicrobial agents, antitumor drugs, and antiviral compounds.

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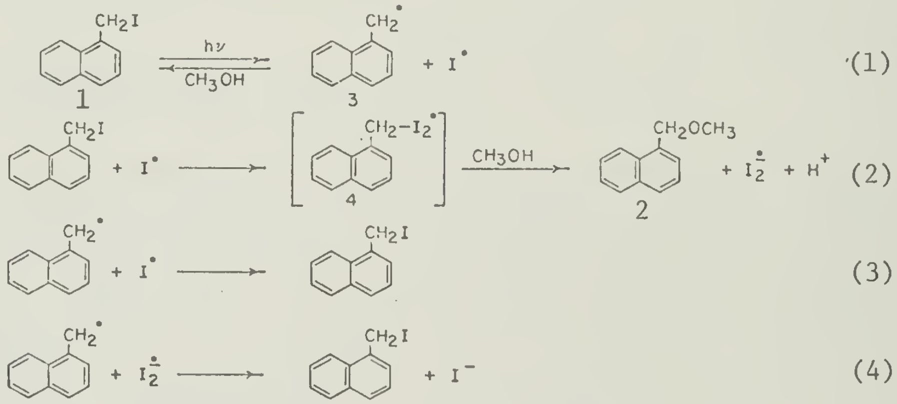
PHOTOLYSIS OF IODOMETHYLNAPHTHALENE:
LASER SPECTROPHOTOMETRIC ANALYSIS OF THE MECHANISM

Reported by Gregory H. Slocum April 6, 1981

The mechanism of photosolvolysis of alkyl halides has been the subject of several recent studies.[1] Kropp and co-workers[2] investigated the photolysis of alkyl iodides and bromides in alcohol solvents in which they observed products characteristic of both radical and carbonium ion intermediates. Kropp has proposed a mechanism in which there is initial homolytic cleavage of the carbon-halogen bond to give a trappable radical pair, followed by electron transfer to produce an ion pair. McKenna and co-workers[3] interpret their data from an investigation of the photosolvolysis of benzyl halides in terms of the interconversion of loose singlet and triplet radical pairs, followed by electron transfer giving an ion pair. Our investigation of the photosolvolysis of 1-iodo-methylnaphthalene 1 in methanol, using nanosecond laser spectrophotometric techniques, has revealed that the reaction product, 1-methoxymethylnaphthalene 2, is formed from a secondary reaction involving photogenerated iodine atoms and the iodide 1.

Scheme I



Photolysis of an oxygen-free methanol solution of 1-iodo-methylnaphthalene 1 gives ether 2 exclusively. Air or oxygen saturation of the solution results in the formation of 1-naphthaldehyde as well as the ether. Irradiation of oxygen-free hexane solutions of 1 shows no net photochemistry. These results are similar to those obtained by others for comparable systems.

Examination of the transient absorption spectrum produced on laser pulse photolysis of 1 reveals three distinct elements in the spectrum. Figure 1(a) shows the spectrum 60 ns after the pulse in methanol. This spectrum with a peak at 368 nm matches the reported spectrum of 1-naphthylmethyl radical 3.[4] If 20% mesitylene is added to the solution, the absorption of the iodine atom-mesitylene complex (λ_{max} 580)[5] can be observed 60 ns after the pulse, Figure 1(b). On a microsecond time scale a third absorption grows into the spectrum. Figure 1(c) shows the difference in the 350-450 nm region of the spectrum between 60 ns and 1200 ns after the laser pulse. This spectrum has a maximum absorption at 390 nm and matches the reported spectrum of $I_2^{\dot{-}}$.[6]

The kinetic behavior of the intermediates responsible for the noted absorptions is inconsistent with mechanisms formerly proposed. If radical 3 and the iodine atom react with each other, then they should be consumed at the same rate. From Figure 2, which shows the rate of decay of the absorption of these two intermediates for a methanol-20% mesitylene solution 4.3×10^{-3}M in iodide 1, one notes that iodine atoms react much faster than does radical 3. Significantly, the $I_2^{\dot{-}}$ absorption appears at about the same rate that the iodine atom-mesitylene absorption decays. Thus, it appears that iodine atoms react with some species to become $I_2^{\dot{-}}$. The identity of this species is revealed by the kinetic behavior of the iodine atoms at varying concentrations of iodide 1. A plot of the observed rate constant for consumption of iodine atoms versus the concentration of 1, Figure 3, shows that as the concentration of 1 increases, so does the observed consumption rate. Photogenerated iodine atoms are reacting with the iodide 1. The rate constant for this reaction, the slope in Figure 3, is $3.5 \pm 0.5 \times 10^8 M^{-1} S^{-1}$.

These results led us to propose the mechanism shown in Scheme 1. The product forming step in this mechanism, eq. 2, is in competition with the recombination of iodine atom and radical, eq. 3. This competition predicts that the quantum yield for ether formation will depend on the concentration of iodide 1. Figure 4 is a double reciprocal plot of the quantum yield for ether formation versus the concentration of iodide 1. As the concentration of 1 increases, so does the quantum yield.

The last step in the mechanism is the reaction of radical 3 with $I_2^{\dot{-}}$ to regenerate 1 and produce iodide ion. The evidence for this step is that the rates of consumption of radical 3 and $I_2^{\dot{-}}$ are approximately the same.

In summary, our kinetic, spectroscopic and product studies indicate the product generating step in these photosolvolysis reactions is a secondary reaction of iodine atoms with the parent iodide. We see no evidence for direct photochemical generation of carbonium ions in our system.

Figure 1

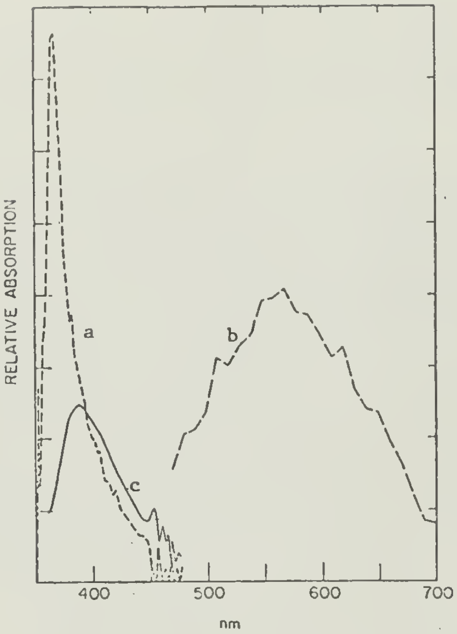


Figure 2

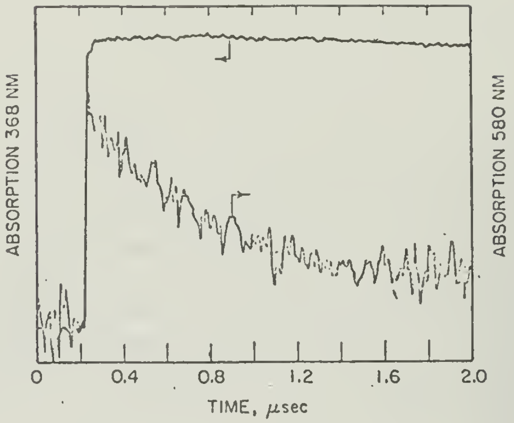


Figure 3

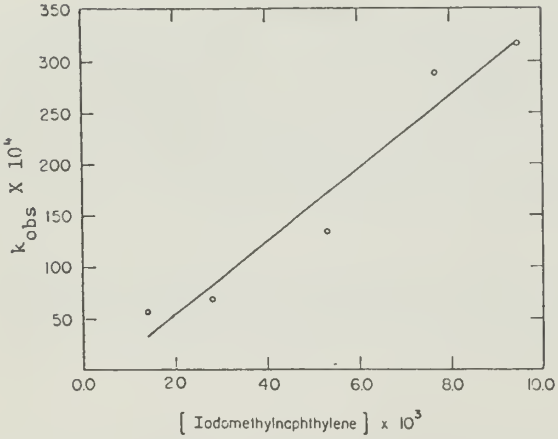
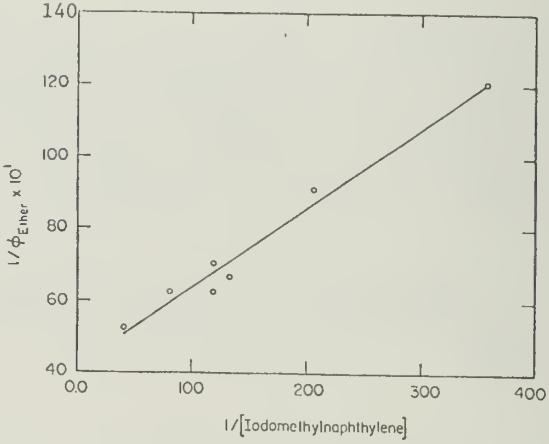


Figure 4



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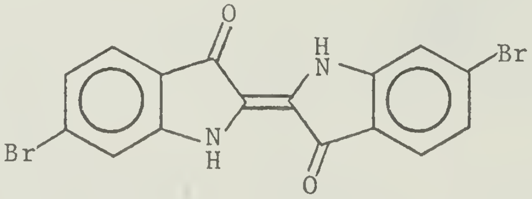
THE INDOLE NUCLEUS IN MARINE NATURAL PRODUCTS

Reported by Adrienne Tymiak April 9, 1981

Naturally occurring derivatives of indole include many biologically essential and pharmacologically interesting compounds (e.g., tryptophan, indole-3-acetic acid, serotonin, reserpine, psilocybin, and the mitomycin family of antibiotics). As a result, the chemical properties of the indole nucleus have been studied extensively.[1,2] One of the first commercially useful marine compounds was an indigoid dye which was assigned structure 1 in 1907.[3] However, not until the last decade have many indoles from marine sources been reported.[4] These marine natural products are typified by unique structures and bioactivities, and, in contrast to terrestrial indole derivatives, are usually halogenated.



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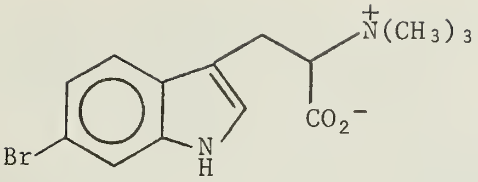
Simple halogenated 2,3-benzopyrroles have been isolated as the odor-producing[5] or antimicrobial[6] constituents in various marine organisms. The halogen substitution patterns about the indole ring system have been determined by comparisons to synthetically prepared compounds.[6,7] Alternatively, NMR techniques based on substituent shielding effects,[8] solvent shifts,[6] and NOE difference spectra[9] have been used to assign halogen positions. These spectral methods have been applied to the structure elucidation of small quantities of brominated antibacterial[10] and antineoplastic[11] marine indoles.

Marine natural products have also provided information about the chemical reactivity of indoles. The pyrolytic behavior of hypaphorine was studied following the observation of mass spectral anomalies in 2, a new sponge-derived amino acid.[12] The reinvestigation of pigments related to 1 showed them to be artifacts of the isolation procedures, and led to the assignment of structures 3 - 6 as the compounds naturally present in molluscs.[13] Derivatization of air sensitive compounds allowed the isolation of a novel chelator[14] (7) and two linear peptides[15] (8 and 9) from a burrowing sponge. In addition, the first examples of marine natural products which are biosynthetically related to terrestrial alkaloids have been extracted from a bryozoan[9,16] (10 and 11) and a blue green alga[17] (12). Other natural products, such as surugatoxin[18] (13) and *Cypridina* luciferin[19] (14), are examples of marine indoles with interesting chemical properties due to other structural features.



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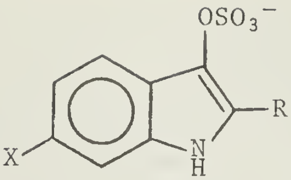
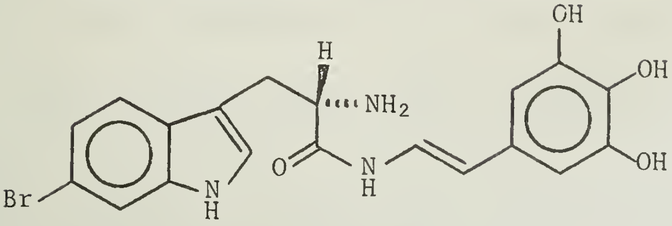


3 X=H R=H

4 X=H R=SCH$_3$

5 •X=Br R=H

6 X=Br R=SO$_2$CH$_3$



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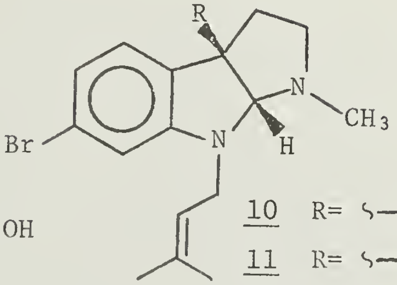
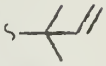
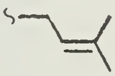
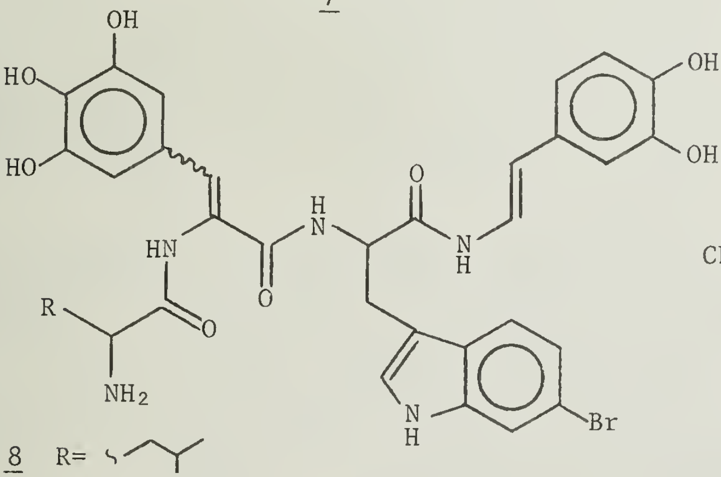
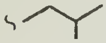
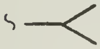


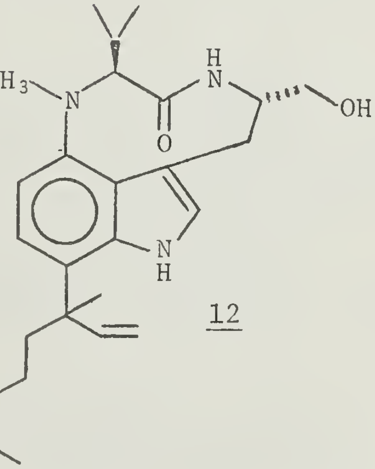
10 R= 

11 R= 



8 R= 

9 R= 



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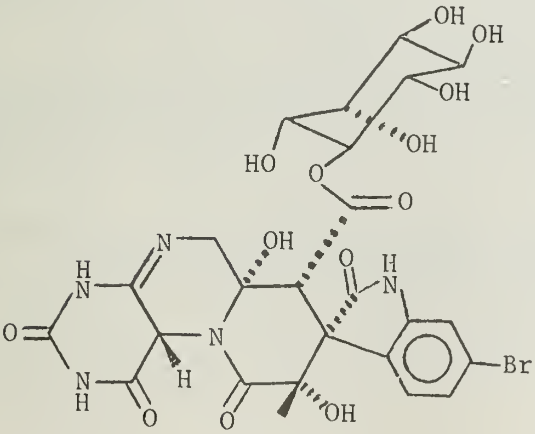

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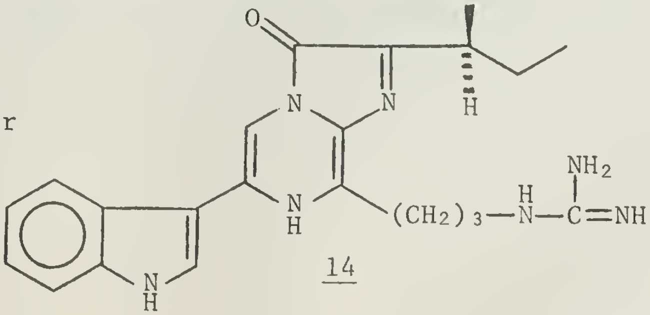

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Approaches to the structure determination of natural products are illustrated by the studies of indoles from marine organisms. These investigations have contributed to the understanding of the chemical, spectral, and biosynthetic properties of the indole nucleus.

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TRIFLUOROMETHYL TRIFLATE: SYNTHESIS AND REACTIONS

Reported by Stephen L. Taylor April 13, 1981

The importance and utility of the trifluoromethylsulfonate (triflate) group has increased significantly in recent years.[1,2] The triflate group is one of the best anionic leaving groups known with solvolysis reaction rates between 10^5 and 10^7 times greater than those of the corresponding tosylates and halides.[3] The triflate anion has a very low degree of nucleophilicity, similar to that of perchlorate or nitrate ions. It has extreme thermal stability and resistance to both reductive and oxidative cleavage.

Alkyl triflates are powerful alkylating reagents and have been reported to alkylate poor nucleophiles such as diethyl ether[4] and benzene[4,5] under mild conditions. Acyl triflates are extremely powerful Friedel-Crafts acylating agents. Effenberger and Epple[6] reported the acylation of even benzene and chlorobenzene in high yield in the absence of Lewis acid catalysts. The recently synthesized trifluoroacetyl triflate[7] is the most powerful trifluoroacylating reagent reported to date. More recently, the halogen (I) triflates, $BrOSO_2CF_3$ and $ClOSO_2CF_3$, synthesized by Des Marteau,[8] have proven to be very powerful electrophilic halogen sources. The triflate groups thus greatly enhances the electrophilic character of the atom to which it is attached.

Until very recently,[8b] the only perfluoroalkyl triflate known was trifluoromethyl triflate (TFMT). Although nucleophilic displacement at carbon of CF_3 is very unfavorable due to shielding by the fluorine atoms, TFMT might be expected to be an electrophilic trifluoromethylating reagent, which would be of great synthetic interest. Surprisingly though, almost no reactions of TFMT have been reported to date. Olah[9a] reports the formation of a quaternary ammonium salt when added to pyridine, but Kobayashi[10] reports that reaction with an enamine gives S-O bond cleavage rather than C-O bond cleavage, one of the first reports of S-O bond scission in alkyl triflates.[11]

Four different methods for synthesizing TFMT have been published. Noftle and Cady[12] first isolated TFMT from the explosive decomposition of bis(trifluoromethylsulfuryl)peroxide, which was produced by the electrolysis of triflic acid.

$$CF_3SO_2OH \xrightarrow[\text{electrolysis}]{-23°} CF_3SO_2OOSO_2CF_3 \xrightarrow{10°} \underset{67\%}{CF_3SO_2OCF_3} + CF_3CF_3$$

Olah and Okyama[9a] synthesized TFMT by the reaction of triflic acid with fluorosulfuric acid.[9]

$$2CF_3SO_2OH + FSO_2OH \xrightarrow[10\text{ hr.}]{165°} \underset{19\%}{CF_3SO_2OCF_3} + CF_3OSO_2F + SO_2 + HF + H_2SO_4 + COF_2$$

Using the expensive reagents CF_3SO_3Ag and CF_3I, Kobayashi et al[10] synthesized TFMT in high yield.

$$CF_3SO_2OAg + 3CF_3I \xrightarrow[C_6H_6]{200°,\ 24\text{ hr}} \underset{86\%}{CF_3SO_2OCF_3} + AgI$$

Most recently, Des Marteau and Katsuhara[8b] have reported the synthesis of perfluoroalkyl triflates, including TFMT, using the highly reactive halogen triflates.

$$CF_3SO_2OCl + BrCF_3 \xrightarrow{-111°} \underset{95\%}{CF_3SO_2OCF_3} + BrCl$$

These routes, however, fail to make TFMT easily and economically accessible. This may account for the paucity of chemical studies of TFMT. Recent studies on the synthesis and reactions of perfluoroalkyl triflates performed in this laboratory[13] will be the main topic of this seminar.

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SYNTHESIS OF 2'-DEOXYNUCLEOSIDES

Reported by Ralph Lessor April 16, 1981

Nucleosides and synthetic analogues of nucleosides have long been of interest to chemists and biochemists due to their presence in RNA and DNA, and in various enzyme cofactors necessary for cellular respiration,[1] as well as the potent antibiotic, antiviral, and antitumor activities displayed by many of the analogues of naturally occurring nucleosides.[2,3] 2'-deoxyribonucleosides, as the subunits of DNA, are of particular interest to those chemists and biochemists who study problems in molecular biology. Synthesis of these nucleosides, and of various analogues of the naturally occurring deoxynucleosides, has posed a continuing problem for chemists.

The normal method of synthesis of ribonucleosides is the condensation of a heterocyclic base, usually as a chloromercuri salt or a silylated derivative, with a protected derivative of D-ribofuranose.[4] In the case of ribonucleosides, such a condensation proceeds with high stereoselectivity to give almost exclusively the desired β-anomer, with little or no formation of the unnatural α-anomer, differing in the stereochemistry of the glycosidic linkage at C-1 of the sugar moiety. This has been attributed to intramolecular participation of the 2-O-acyl group generally employed on the sugar derivative. In attempts to synthesize 2'-deoxynucleosides by a similar method, the absence of such participation leads to a mixture of anomers, in which the undesired α-anomer usually predominates.[5-7]

The attempts that have been made to convert ribonucleosides into 2'-deoxyribonucleosides have met with only moderate success. Direct nucleophilic displacement at C-2' of nucleosides has been shown to be inhibited by both steric and electronic factors.[8] Therefore, many attempts at deoxygenation have relied on intramolecular processes to remove the 2' hydroxyl group.

The cyclonucleosides formed by treatment of a mixture of 2'- and 3'-O-tosyl-8-bromoadenosines with thiourea can be reductively cleaved to give 2'- and 3'-deoxyadenosines, but in very low overall yields.[9] Ring opening of a 2', 3'-bridged acyloxonium intermediate with halide ion followed by reductive dehalogenation affords 2'- and 3'-deoxynucleosides,[8,10,11] but with a strong preference for the 3'-deoxy isomer. Hydrogenation of a 1', 2'-unsaturated 2'-deoxynucleoside leads to the 2'-deoxynucleoside, but once again in very low yield.[12] In an attempt to use a preformed, easily-removed C-2' substituent that would still exhibit the same directing effect, a protected 2-thioribose derivative was condensed with a silylated purine, and the resulting 2'-thionucleoside was desulfurized with Raney nickel, giving 2'-deoxyadenosine in a rather disappointing 8% yield.[13]

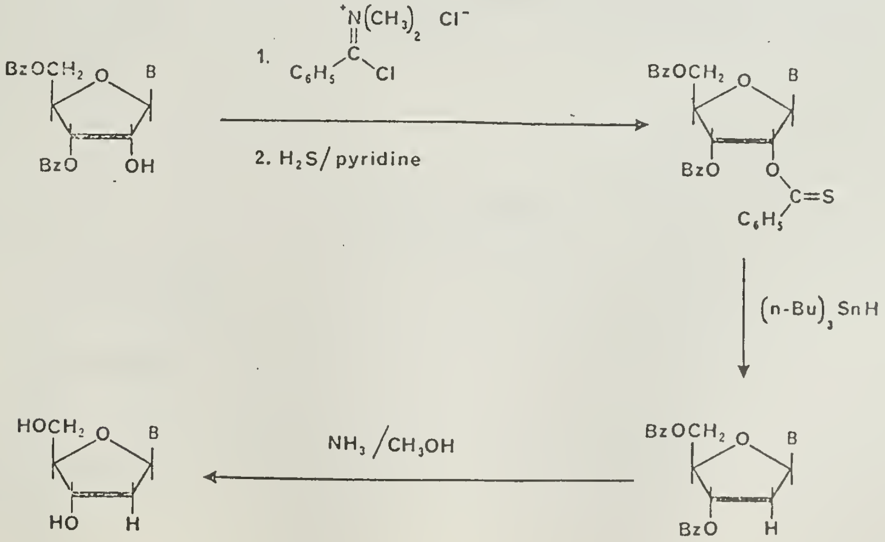
In order to circumvent these problems inherent in 2'-deoxyribonucleoside synthesis, a method has been developed for the conversion of ribonucleosides into their 2'-deoxy analogues. In view of all the problems previously observed during attempts at heterolytic cleavage of the C-2' carbon-oxygen bond, the homolytic cleavage of a 2'-O-thiobenzoyl nucleoside was chosen.

Barton and coworkers have reduced a 2',3'-di-O-thiocarbonate derivative of adenosine to a mixture of 2'- and 3'-deoxyadenosines in good yield during studies directed toward glycoside antibiotic synthesis.[14] A recent communication describes a similar reduction of 2'-O-phenylthiocarbonate derivatives of nucleosides which overcomes the regioselectivity problem encountered by Barton.[15]

Suitably protected nucleosides were prepared by regioselective deacylation of fully acylated nucleosides using hydroxylaminium acetate in dry pyridine.[16] This approach seems particularly appropriate for the synthesis of unnatural nucleoside analogues, since fully acylated nucleosides result from the ribosidation of synthetic heterocycles. Whether the observed selectivity is due to the conversion of the 2',5'-di-O-acyl nucleoside into the 3',5'-isomer upon chromatography,[16] or to the selective crystallization of the 3'-5'-di-O-acyl isomer out of an equilibrating mixture, as suggested by data on acyl migration in such systems,[17] is not clear, but the 3'-5'-di-O-acyl isomer is obtained in 60-75% yield.

3'-5'-di-O-benzoyl nucleosides obtained in this manner were thiobenzoylated under the mildest conditions possible to minimize further acyl migration before reaction. Treatment with the chloroiminium chloride derived from N,N-dimethylbenzamide, followed by hydrogen sulfide/pyridine, gave the 3',5'-di-O-benzoyl-2'-O-thiobenzoyl nucleosides in 75-80% yields. Reductive cleavage of the thiobenzoyl group with tributyl stannane in refluxing toluene afforded acylated 2'-deoxynucleosides in 85-90% yields (see Scheme I).

Scheme I



Further studies on the application of this method to the synthesis of fluoroescent analogues of 2'-deoxyadenosine, and to the synthesis of 3'-deoxy- and 2',3'-dideoxy-nucleosides are under way.

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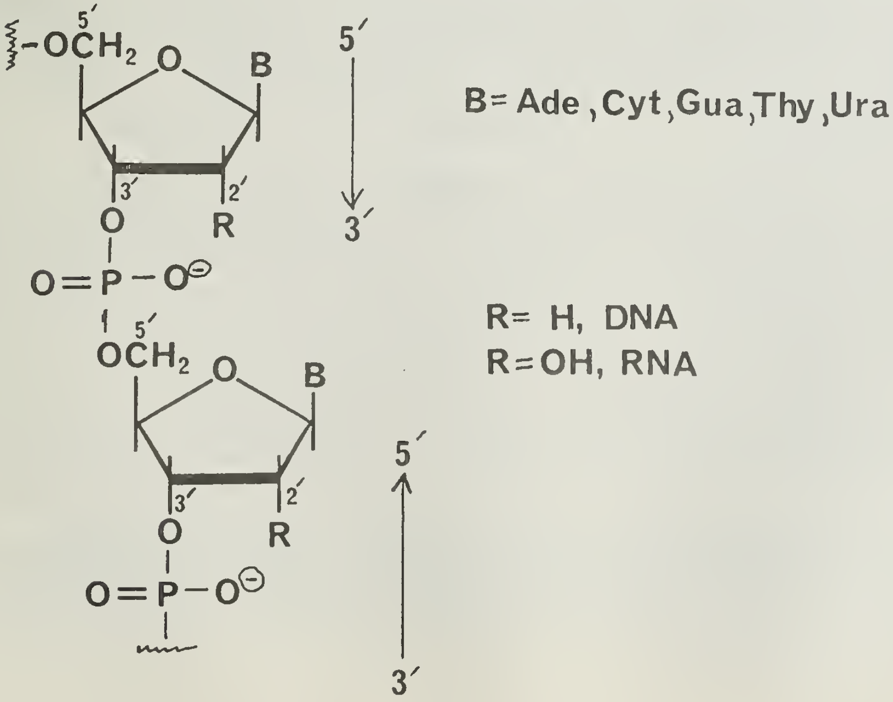
CHEMICAL SYNTHESES OF OLIGONUCLEOTIDES ON SOLID SUPPORTS

Reported by Dee Ann Casteel April 20, 1981

Attempts to develop a successful methodology for synthesizing sequence specific oligonucleotides have been numerous.[1] With the rapid development of molecular cloning and other nucleic acid research, the need for efficient, defined oligonucleotide synthesis is obvious. Recent successes include synthesis of the lactose operator of E. coli,[2] the human insulin genes,[3] tRNA fragments,[4] some containing hypermodified bases,[5] and, using RNA ligase to join large oligomers, the entire E. coli formylmethionine-tRNA.[6] Existing solution methods are laborious and time-consuming in operation due to the problems of sequence specificity, regiospecific 3',5'-coupling, labile phosphodiester linkages, and numerous possible side reactions involving the sugar, phosphate, and base moieties. Isolation, purification, and verifaction of sequence demand great care. Current work has led to improved solution techniques which have been applied to the intrinsically more rapid solid-phase syntheses[7] and finally to automated oligonucleotide synthesizers.[8]

The nucleic acids, DNA and RNA, are polymers of nucleotides linked through a 3',5'-phosphodiester bond (Fig. 1). Chemical synthesis has been approached from several strategies. A stepwise addition of monomeric units to the growing chain is the most obvious route but often a block (or convergent) synthesis makes better use of material. The chain can be elongated in either direction, 5'→ 3' or 3'→ 5', depending on the protection scheme chosen. On a solid phase, direction depends on which end is connected to the support. In theory, the phosphate group for formation of each phosphodiester bond could be on either the 5'- or the 3'-end but most workers seem to prefer a 3'-phosphate because of the relative ease of selectively protecting the 5'-hydroxyl and better yields.[9]

Figure 1



The units added to the growing polymer can be monomers, dimers, trimers, or larger, but all must be suitably protected so that other functionalities on the nucleotide do not react under the conditions used for coupling. The base residues thymine and uracil are often used in methodology studies because these pyrimidine rings do not need to be protected. Adenine, guanine, and cytosine have exocyclic amine groups which are capable of reacting to form phosphoramidates during phosphorylation.[1a] All three residues are most commonly protected with N-acyl groups: benzoyl for adenine and cytosine and isobutyryl for guanine although others have been reported.[1] Recent procedures note that under certain conditions, these residues need not be protected.[10] Deacylation is readily effected by ammonolysis.

Protection of the ribose and deoxyribose sugars are more complicated. It would be desirable to be able to selectively protect and then selectively deprotect each position, 3', 5', and in the ribose cases 2'. The 5'-position is the easiest to selectively protect because it is the only primary hydroxyl. In most examples, monomethoxytrityl or dimethoxytrityl groups are used on the 5'-end.[11] Deprotection goes quickly and in nearly quantitative yields in 2% benzenesulfonic acid. A problem with acidic treatment is that the glycosidic bond of purines and especially protected purines is acid labile.[12] Recently, it was found that $ZnBr_2$ will remove methoxytrityl groups with negligible depurination.[13] A new 5'-protecting group, o-dibromomethylbenzoyl, has been reported by Reese to be removable by treatment with $AgClO_4$ and collidine followed by morpholine.[14] The 3'-hydroxyl, if not carrying the phosphate group, is generally protected with the base labile acetyl group.[1]

The 2'-hydroxyl presents the most problems for selective protection/deprotection and for this reason ribonucleotide synthesis has lagged behind deoxyribonucleotide work. The chosen group must be stable to all reaction conditions but be sufficiently labile to be removed at the end of the synthesis without cleaving the internucleotide bonds. Benzyl,[1] tetrahydropyranyl,[1] methoxytetrahydropyranyl,[15] levulinyl,[9b] tert-butyldimethylsilyl,[16] and o-nitrobenzyl[17] groups have been used successfully. The most promising of these is the o-nitrobenzyl group[17] which can be removed by photolysis and the alkylsilyl group[16] which is removed by treatment with fluoride ion. Fluoride also causes ca. 10% cleavage of phosphotriesters but does not degrade diesters.[18]

Three main types of nucleotide coupling procedures have been developed. The phosphodiester approach was introduced in 1956 by Khorana and co-workers (Fig. 2).[19] A protected phosphomonoester is reacted with a partially-protected nucleoside in the presence of a coupling agent such as dicyclohexylcarbodiimide or aryl sulfonyl chlorides. Although this method is still used occasionally, it suffers from several problems. The phosphodiester functions are nucleophilic and subject to attack in subsequent phosphorylation steps. The ionic nature of the diester eliminates the use of many standard organic purification techniques, such as adsorption chromatography. Ion-exchange chromatography can be used but the pH must be carefully controlled to prevent hydrolysis.[1]

In order to circumvent these difficulties, Letsinger developed two new methodologies in the mid-1960's. His phosphotriester approach has virtually replaced the diester method (Fig. 3).[20] By esterifying the third site of the phosphate, all of the problems of the diester method are removed. The phosphate protecting group (R') must be chosen so that it can be selectively removed at the end of the synthesis without harming the internucleotidic bonds. Much work has focused on finding an adequate phosphate protecting group. Among groups reported as phosphate protecting groups are substituted phenyls,[19a,21] benzyl,[22] methyl,[23] cyanoethyl,[24] trichloroethyl,[25] and 8-quinolyl.[26] Pfleiderer recently reported the use of the *p*-nitrophenylethyl group which upon deprotection with DBU gave no detectable side products.[27]

Figure 2

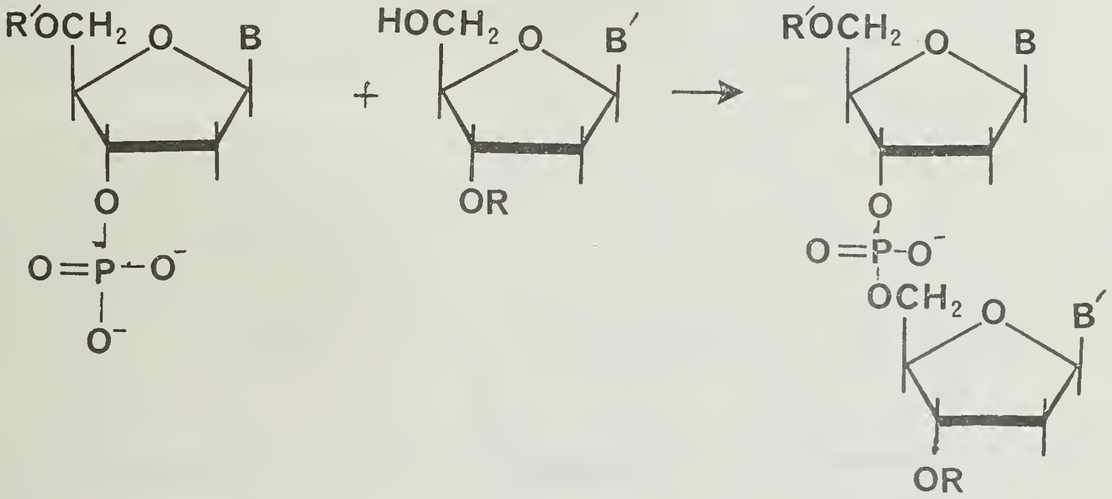
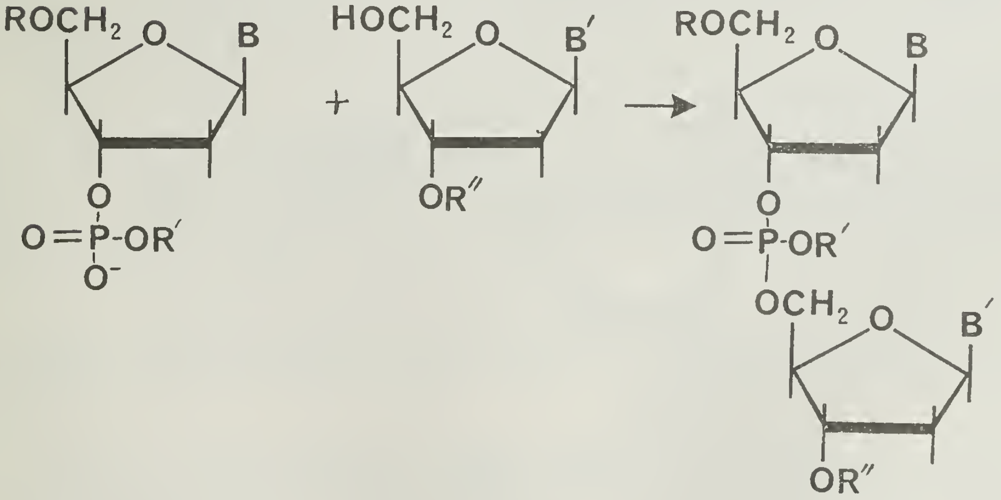


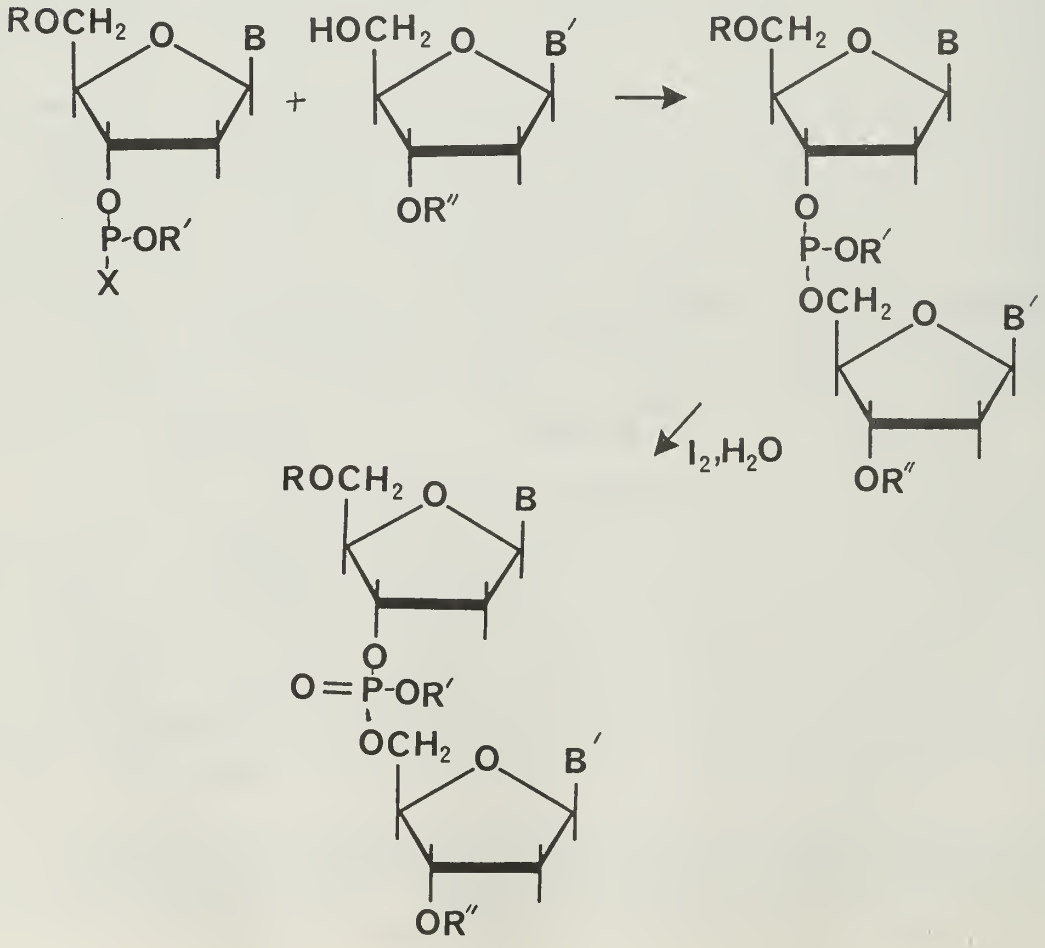
Figure 3



The phosphotriester method requires two phosphorylation steps for each internucleotidic bond. The first involves phosphorylation generally of a monomer with an activated phosphomonoester. A monofunctional reagent such as *p*-chlorophenyl N-phenylchlorophosphoramidate[28] is preferred to avoid the formation of symmetrical dinucleotides. The apparently bifunctional p-chlorophenyl phosphorodi-(1,2,4-triazole) reacts to give only diesters when used in excess, however.[29] The second phosphorylation leads to internucleotide bond formation and requires a coupling agent. Reagents such as mesitylenesulfonyl chloride and triisopropylbenzenesulfonyl chloride (TPSCl) have been used but low yields and sulfonated side products were undesirable.[30] A study of various arylsulfonyl chlorides, triazoles, and tetrazoles has shown that optimization of yields with little sulfonation is achieved using TPSCl with added tetrazole.[31]

The last method used frequently involves a phosphite intermediate for the coupling reaction followed by oxidation to the phosphate (Fig. 4)[10b] Phosphite reactions are faster than the corresponding phosphate reactions because the leaving groups on phosphorus (III) are more reactive.[8] Also, phosphite couplings do not require a coupling agent. The phosphite intermediates are stable enough to isolate as shown in a recent trinucleotide diphosphite synthesis by Letsinger.[32]

Figure 4



In light of Merrifield's success with solid-phase peptide synthesis,[33] experiments were begun on the application of solid support systems to oligonucleotide synthesis. Letsinger employed a substituted polystyrene resin,[34] to which the first deoxynucleoside (A,G, or C) was attached through its exo amino group. Yields in coupling, however, were too low to be practical. Gait and Sheppard reported the synthesis of d(TpGpGpCpCpCpApT)[35] on a polar polydimethylacrylamide resin using a stepwise phosphodiester approach in an overall yield of ca. 0.5%.[36] By adopting the phosphotriester method to an improved resin,[37] they were able to achieve isolated yields of up to 7.8% for octamers and 2.5% for dodecamers.[36] For these syntheses, the first 5'-protected nucleoside is succinylated at the 3'-end and reacted with free amino groups on the resin. The linkage is stable in pyridine and under acidic conditions but is cleaved rapidly by ammonia or aqueous NaOH. The nucleotide assembly is accomplished by shaking reagents with the resin-bound polymer followed by washing and repetition of the cycle. This work was done on a modified peptide synthesizer.

Itakura and co-workers have reported success with a polyacrylmorpholide support using a phosphotriester block strategy.[38] The linkage to the resin is essentially the same as that used by Gait and Sheppard. Yields for each coupling step are above 90%. The use of trimers or dimers rather than monomers limits the number of coupling steps necessary but requires more steps for the synthesis of the blocks. Purification is also simplified in the block approach as chain lengths will differ by two or three rather than one nucleotide.

Polystyrene resins were at first thought to be inappropriate for polynucleotide synthesis,[35a,38] but Itakura has shown that they may have some advantages over the more polar resins.[39] Polyamide resins, due to their high affinity for hydroxylic solvents, must be scrupulously dried at every new addition of a nucleoside residue. This time-consuming step is greatly reduced using a 2% cross-linked divinylbenzene support. He reported a 34% overall yield on polystyrene of a hexadecamer using block trimer compared to a 40% yield on polyacrylmorpholide.

A synthesis of oligothymdilic acids (up to a 25-mer) has been reported using a unique resin-polymer linkage on a cellulose support.[40] A 5'-ribonucleotide is bound to the cellulose and the deoxyribonucleotides are added to the 3'-end. Cleavage of the ribo-deoxyribo internucleotide bond results in the release of the deoxy polymer with concomittant formation of a 2',3'-cyclicribonucleotide.

The phosphite method has also been adapted to solid support synthesis. A nonamer was synthesized in 25% yield overall using a macroporous silica gel support.[41]

The most recent advance in oligonucleotide synthesis has been the adaptation of solid support methods to automatic synthesis instruments. Several companies are employing various chemical strategies to assemble DNA sequences automatically. Bio Logicals, a Toronta based company, will begin delivery of their $29,500 instrument in April, 1981.[42] Using Ogilvie's phosphite methodology, the machine is reported to be able to add a base to the polymer every 30 minutes and is preset to synthesize a minimum of 50 mg of any dodecamer. The user chooses the appropriate pre-packed column, which contains the solid phase with the first base already attached. The desired sequence is then specified on a program card. Reagents and solvents are pumped in sequence through the column. Protected monomers, reagents, and solvents come prepackaged for easy connection to the system. The instrument design is highly dependent on the chemistry and use of the instrument requires no chemical knowledge.

The other instrument currently on the market is produced by Vega Biochemicals in Tucson.[43] Although more expensive ($49,500), this system is much more flexible and was designed so that new advances in chemistry could be easily incorporated. The machine can use phosphite or phosphotriester methodology. The system uses a shaken reaction vessel with fritted glass top and bottom rather than a column. Programming of the sequence is accomplished by keyboard input to a microprocessor. Cycle time for addition of a nucleotide is three hours.

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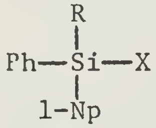
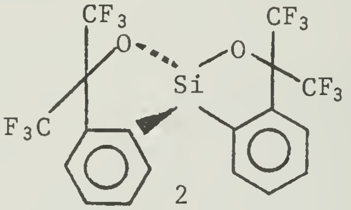
INTRAMOLECULAR LIGAND EXCHANGE AT TETRACOORDINATE SILICON

Reported by William Stevenson April 23, 1981

Intramolecular ligand exchange at tetracoordinate (8-Si-4)[1] silicon has been most extensively studied in the racemization of substituted silanes in the presence of weak nucleophiles.[2,3,4] Ionization to a silicenium cation does not appear to be a mechanism for the racemization.[2b,e,h,i,3] For chloro- and bromosilanes such as 1, racemization is second order in the nucleophile and shows a strongly negative activation entropy for the reaction.[2a-d] These results are consistent with a mechanism which involves reversible formation of a pentacoordinate silicon intermediate followed by attack of a second molecule of nucleophile in the rate determining step to give either a symmetrical octahedral (12-Si-6) intermediate or a pentacoordinate (10-Si-5) species (Scheme).


$Ph{-}Si(R)(1\text{-}Np){-}X$

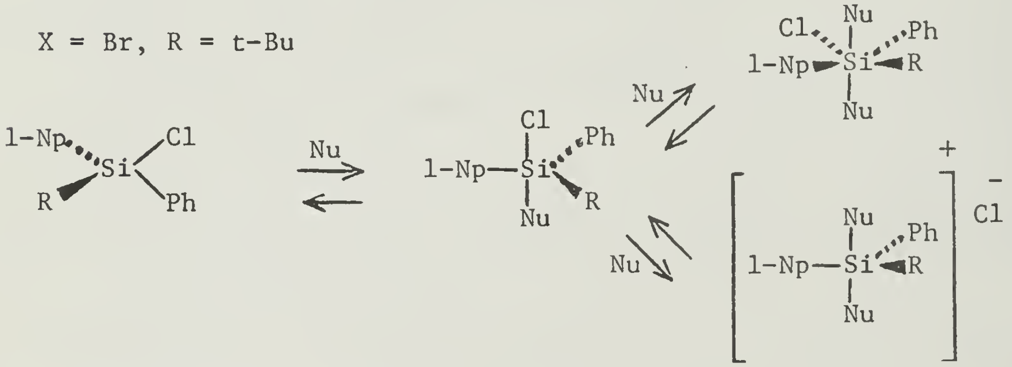
1



2

X = Cl, R = Me, Et, i-Pr, o-menthyl

X = Br, R = t-Bu



Scheme. Racemization of Chlorosilanes.

Racemization of fluoro- and aminosilanes has also been observed in nucleophilic media.[3,4] Interpretation of the kinetic findings is somewhat difficult as racemization is third order (or higher) with respect to the nucleophile. One mechanism which has been considered involves attack of one molecule of nucleophile to give a pentacoordinate (10-Si-5) intermediate which undergoes inversion by a series of pseudorotations followed by loss of the nucleophile.[3a] Although this mechanism is not consistent with the above mentioned kinetic evidence, it should be considered in other cases, as pseudorotation is believed to occur in certain stable 10-Si-5 species (e.g., SiF_5^-).[5]

Recent kinetic studies on intramolecular ligand exchange have been performed on 2.[6] This molecule is unusual in that its bidentate ligands are of a type specifically designed to stabilize hypervalent species,[7] and in fact 2 does form stable 10-Si-5 compounds with a variety of strong nucleophiles. Kinetic studies on the inversion of 2 (evidenced by interconversion of the diatereomeric trifluoromethyl groups) in weakly nucleophilic solvents have indicated a first order dependence on the nucleophile.[6] Pseudorotation of a pentacoordinate intermediate would seem a likely mechanism in this case, but the exact sequence of intermediates has not been established. Although pentacoordinate intermediates (usually trigonal bipyramidal) have been generally invoked to explain substitution reactions at tetrahedral silicon, the stereochemical mode of attack is still very much in question.[8]

A final mechanism for inversion at tetrahedral silicon involves a twisting of ligands through a planar transition state, the possibility of which has been suggested by recent theoretical and experimental work.[9] Preliminary studies on 2 in nonnucleophilic solvents indicate that slow inversion does in fact occur.[6] Some support for a mechanism of inversion through a planar transition state is given by the crystal structure of 2 which shows distortions towards planarity.

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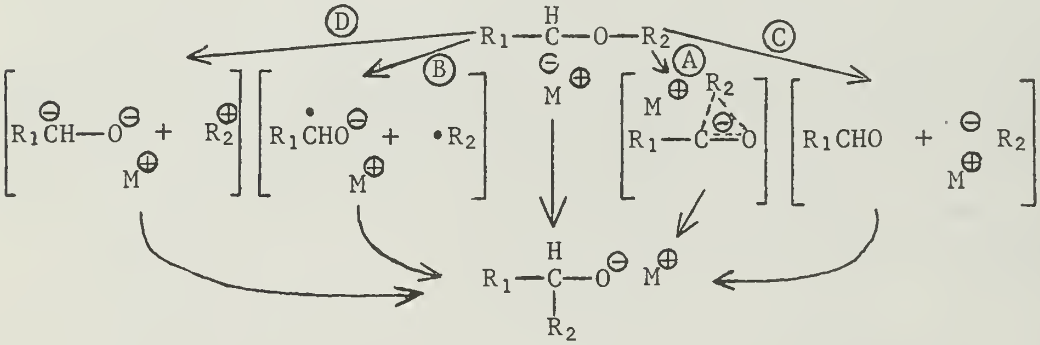
THE WITTIG REARRANGEMENT

Reported by Bruce J. Kokko April 27, 1981

The Wittig rearrangement is a well known reaction in organic chemistry.[1] In 1928, Schlenk and Bergmann observed the rearrangement of sodium benzhydral methyl ether to diphenylmethylcarbinol.[2] Wittig and coworkers later observed the same phenomenon with lithiated benzylmethyl ethers.[3] The Wittig rearrangement is, then, the rearrangement of an α-metallated ether to the corresponding alcohol:



D
B
A
C
$R_1-\overset{H}{C}-O-R_2$
$M^\oplus$
$R_1\overset{\ominus}{C}H-O^\ominus + R_2^\oplus$ $M^\oplus$
$R_1\dot{C}HO^\ominus + \cdot R_2$ $M^\oplus$
$M^\oplus$ R_2 $R_1-C=O$
$R_1CHO + {}^\ominus R_2$ $M^\oplus$
$R_1-\overset{H}{C}(R_2)-O^\ominus M^\oplus$

R_1 can be any group that will stabilize a negative charge. Such groups are benzyl, phenacyl, benzhydral, allyl, 9-fluorenyl, etc.[1c] R_2 can be a variety of functions (vide infra).[1c]

Considerable energy has been directed toward the elucidation of the mechanism of the Wittig rearrangement.[4] Several paths have been postulated (see above). Lansbury and Pattison found that benzylcyclobutyl and cyclopropyl ethers rearrange, without isomerization of the migrating group, to the corresponding carbinols in 90% yield.[4d,e] These observations coupled with the fact that adamantyl ethers but not benzylnorbornyl ethers rearrange, suggested that paths A and B are the most likely mechanisms. By examining the reactions of chiral s-butylethers, Schöllkopf and workers were able to study the stereospecificity of the Wittig rearrangement.[4c] They observed racemization as high as 80%. This suggested that a concerted path A is not very likely. The most definitive study in this area was completed by Garst and Smith.[4g,h] They compared the Wittig rearrangement with reactions where radicals are known to be involved.[5] Garst suggests that path B is most consistent with their data, and the data of the earlier, less definitive experiments.

As earlier alluded, R_2 can be varied considerably. In the alkyl series, ease of migration parallels radical stabilities; $CH_3 < 1° < 2° < 3°$.[1c,d,4f,e] Side reactions involving α',β-eliminations are serious problems in primary systems.[4e] However, the rearrangement of tertiary and secondary ethers affords the desired alcohols in yields of 35 - 63%. Buchi has examined the Wittig rearrangement of vinyl benzyl ethers.[6]

He found that rearrangement proceeds smoothly to give the desired vinyl carbinols in 85% yield. Furthermore, the rearrangement occurs with complete retention of the double bond geometry. The rearrangement of allyl ethers have also been studied.[7] These systems rearrange, by the most part,[8] via the thermally allowed [2,3] sigmatropic shift. Benzyl ethers rearrange in high yields.[1] Phenyl groups migrate to give carbinols in high yields; however, α-elimination of phenoxide can be a problem.[9] Alkynyl groups compete for site of metallation; consequently, the yields of desired carbinols are low.[7c]

A few amine[10] and allylic sulfide[11] systems have been reported to undergo Wittig-like rearrangements.

The Wittig rearrangement, though interesting, has not been exploited synthetically since the target alcohols can usually be prepared by more convenient methods. In this seminar a possible application of this process shall be proposed. This application could be very useful synthetically.

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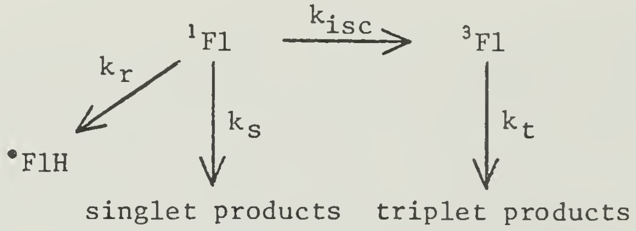
THE CHEMISTRY OF FLUORENYLIDENE

Reported by Peter B. Grasse April 30, 1981

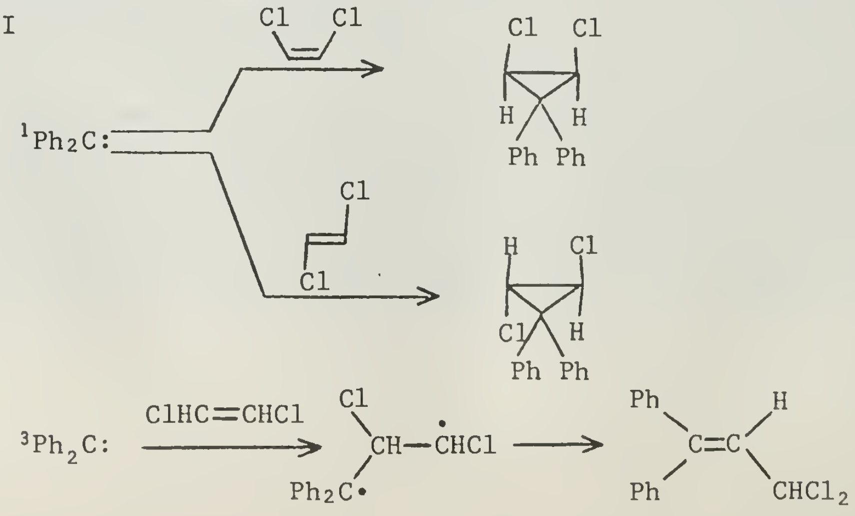
The advent of spectroscopic techniques capable of observing intermediates with nanosecond lifetimes has sparked interest in the chemistry of carbenes.[1] The reactions of these intermediates may be classified in terms of addition to multiple bonds or insertion into single bonds. The question of spin multiplicity is central to understanding the chemistry of these divalent carbon species as classically each state exhibits characteristic reactivity. The triplet state of most aryl carbenes has been shown by spectroscopic methods to be the ground state.[2] The mechanistic details concerning carbenes in solution have been gleaned from extensive product studies. The Skell Hypothesis[3] has been employed to estimate the composition of reacting spin states based on the stereospecificity observed in cyclopropanation reactions. This analysis neglects the possibility that complete reaction by the singlet carbene with an olefin may occur before intersystem crossing produces significant amounts of triplet carbene. Figure I illustrates these possibilities for fluorenylidene (Fl).

Figure I



The reaction of fluorenylidene with olefins produces predominantly cyclopropanes with only slight amounts of allylic C-H insertion products.[4] Jones and Rettig[5] showed the stereospecificity of the cyclopropanation to be dependent on the amount of hexafluorobenzene(HFB) present. Their analysis concluded that with more inert moderator/dilutent (HFB) present the less specific addition was due to a greater participation of the triplet carbene. 1,1-Dicyclopropylethylene[6] and 1,2-dichloroethylene[7] have been used as substrates to monitor reacting spin states. It is believed cyclopropanes result from addition of the singlet carbene, while rearranged products result from triplet addition as shown in Figure II. Direct spectroscopic observation by Zupancic and

Figure II

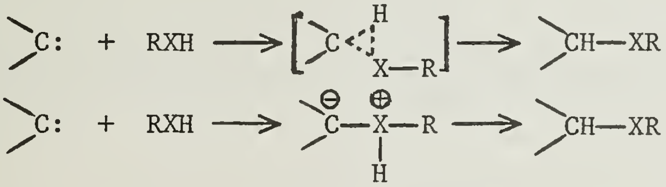


Schuster[8] of singlet and triplet fluorenylidene allowed measurement of the singlet-triplet intersystem crossing rate constant (k_{isc}), and the rate constants for singlet (k_s) and triplet (k_t) reactions with various substrates. Analysis of the stereospecificity of the addition of fluorenylidene to several olefins in acetonitrile solution in light of the measured rate constants and olefin concentrations shows an apparent contradiction with Skell's Hypothesis.[9]

To examine this interesting result further we have undertaken the study of the reactions of fluorenylidene in several solvent systems. Solvent choice is greatly limited by the extreme reactivity of fluorenylidene and the present limitations of our spectroscopic apparatus. The carbene behavior observed in spiropentane, cyclopropane, and Freon 113 are in qualitative agreement with the acetonitrile results, though complications arise due to carbene reactions with the solvent or spurious impurities. It is interesting to note that the lifetime of the singlet carbene is longer in the less polar solvents.

Investigation of the reaction of fluorenylidene with nucleophiles has been undertaken to attempt to discern if the reaction proceeds by direct insertion into a hydrogen-heteroatom bond or through formation of an intermediate ylide[10] as shown in Figure III. Kinetic and product isotope effects point to the direct insertion mechanism for reactions with alcohols while thiols appear to go through the intermediate ylide. In the reaction with amines we believe the formation of the ylide may be reversible to regenerate carbene. As a result of reversible ylide formation the yield of secondary amine is low and the kinetics are difficult to study. Further work is underway.

Figure III



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SOLVENT AND SOLVENT DEUTERIUM ISOTOPE EFFECTS ON THE LIFETIME OF SINGLET OXYGEN IN SOLUTION

Reported by John R. Hurst May 4, 1981

Singlet molecular oxygen has been the object of intense interest because of its high reactivity toward olefins,[1,2] aromatic hydrocarbons,[3] and various other classes of organic compounds.[4,5] Common in much of the literature on dye sensitized photooxidation with singlet oxygen is the recognition that the efficiency of photooxidation is dependent on the solvent.[1,3,6,7] The most amazing solvent effect is found on comparison of the lifetime of singlet oxygen in protiated solvents to that in their perdeuterated counterparts.[8,9]

One method of determining the kinetics of singlet oxygen decay which was developed by Merkel and Kearns[10] utilized a laser pulse to excite a solution containing a dye which sensitizes singlet oxygen (typically methylene blue) and a colored substrate which quenches singlet oxygen to form a colorless adduct (typically 1,3-diphenylisobenzofuran). According to measurements made by monitoring the absorption of the quencher, the lifetime of singlet oxygen ranges from 2 μsec in water to 700 μsec in carbon tetrachloride.[9,10,11,12,13,14,15,16,17,18,19]

This method of monitoring singlet oxygen encountered several drawbacks, including the fact that singlet oxygen is not the only species capable of reacting with the quencher to form colorless products. Also, Foote et. al.[8] have measured a deuterium isotope effect for acetone of 16, which is inconsistent with the isotope effect of 1 measured by Kearns et al.[9]

TABLE 1

	Kearns et. al[9,11]		Foote et. al.[8]	Byteva et. al.[28]	Schuster and Hurst[21]		
Solvent	τ_H(μs)	τ_D(μs)	τ_D/τ_H	τ_H(μs)	τ_H(μs)	τ_D(μs)	τ_D/τ_H
CCl_4	700	—	—	26,000	12,000	—	—
$CHCl_3$	60	300	10	250	222	1450	6.5
Acetone	26	26	16	51	54	380	7.0

Byteva and coworkers[20] and our laboratories[21] have developed independently a germanium photodiode detector which can detect the known singlet oxygen phosphorescenece at 1270 nm[22,23,24,25,26] and has the time resolution necessary for pulse spectroscopy. Our apparatus employs optimized optics, a near IR monochromater and filter, and a transient digitizer to analyze the signal from the germanium detector, which detects the phosphorescence at a 90 degree angle to the exitation beam. The exitation source is a 70 mJ dye laser (580 nm, 300 nsec. pulse) which is used to excite methylene blue, rose bengal, or tetraphenylporphorin. Using this setup we were able to monitor the decay of singlet oxygen in solution, and our results are consistent with those of Byteva *et. al.*[28] but not Kearns *et. al.*[9] (see Table 1). Of particular interest is the contribution of a significant second order effect due to the annihilation of two singlet oxygen molecules,[27] which was not treated by Kearns *et. al.*[9,10-11,12,13] or other workers using Kearns' technique.[14,15,16,17,18,19]

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ORGANIC SEMINAR ABSTRACTS

1981-82, Semester II

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1,3- AND 1,4-DEHYDROBENZENE

Reported by Gene Garrett January 18, 1982

The isomeric dehydrobenzenes 1, 2, and 3 have been the subject of theoretical and experimental investigations since they were first proposed as organic reactive intermediates.[1] Of the three possible isomers, only the 1,2-dehydrobenzene (1) has been extensively studied. Dehydrobenzene 1, commonly called benzyne, has been generated and characterized spectroscopically[2] in an argon matrix at 8K and the ground state of 1 was found to be a singlet. The reactivity of 1 toward a variety of substrates has been examined[1] and the chemistry of 1 found to be typical of a highly strained acetylene. The subjects of this review are the less well-known species 1,3-dehydrobenzene (2) and 1,4-dehydrobenzene (3).

There are a number of possible formal structures for 2 and 3 as illustrated in Figure 1. The biradicals 2a and 3a could exist as a singlet or triplet in the ground state depending upon the degree of interaction between the dehydro centers.[3] The energy of the biradicals 2a and 3a relative to the bicyclics 2b and 3b is uncertain. The latter have one additional carbon bond but also would possess considerable strain energy. If in fact 2a and 3a are of lower energy than 2b and 3b, the latter will belong to an unusual class of compounds possessing a negative bond energy.[4] Alternatively, 2a and 2c could be considered as resonance structures of 2b and 3a and 3c-e could be considered as resonance structures of 3b. The species 3b could be considered destabilized by the 4nπ cyclobutadiene system or be viewed as stabilized by the overall (4n + 2)π electron system.

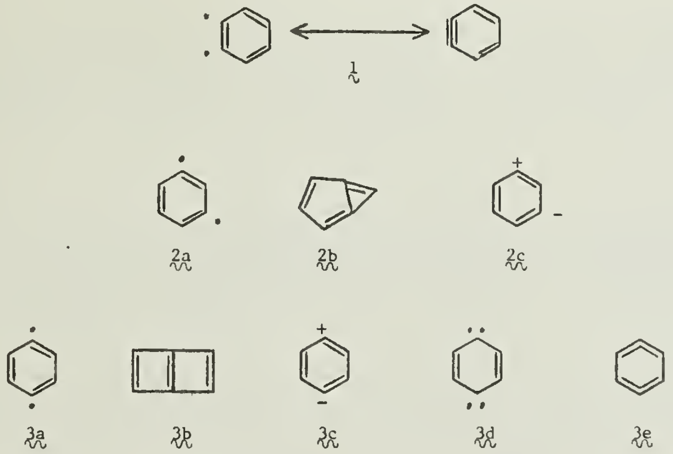


Figure 1. Proposed Structures for 1,2-Dehydrobenzene (1), 1,3-Dehydrobenzene (2), and 1,4-Dehydrobenzene (3)

Theoretical and experimental studies of 2 and 3 have been carried out in attempts to answer these structural questions. Various Hückle, ab initio and geometry optimized calculations have been reported for 2 and 3. Theoretical interest has centered on the ground and excited state multiplicities, energies, and geometries of 2 and 3. Due to expected high reactivity, 2 and 3 have been sought experimentally as fleeting intermediates in thermal and photodecompositions of disubstituted benzenes, in gas phase and solution pyrolyses of substituted cis-hexa-1,5-diyn-3-enes, and in base promoted dehydrohalogenation of bicyclic substrates.

Theoretical Treatments. Despite the interest in 2 and 3,[5] few meaningful theoretical studies have been reported. Dewar and Li[6] reported the first geometry optimized calculations for the dehydrobenzenes. The MINDO/3 method revealed a single energy minima for 2 corresponding to a singlet ground state best represented by structure 2b. The same treatment predicted two energy minima

for 3. Structure 3b was calculated to lie in a shallow local energy minima 19-36 kcals/mole above 3a. The calculated enthalpy for the conversion of 3b to 3a was ~5 kcals/mole. The ground state of 3 was predicted to be a singlet with a small singlet-triplet separation. The most interesting result of this study was that singlet 2a and 1 were predicted to be of similar stability.

In conjunction with experimental work on 2, Washburn, *et.al.*,[7] performed geometry optimized calculations on 2 using STO-3G basis with Gaussian 70. According to this approach, the optimun singlet was best represented as 2a. The same structure was predicted to be at an energy minima using the 4-31 basis set. SCF calculations with STO-3G or 4-31 basis set and CI predicted singlet 2b for the ground state. Washburn predicted, that in the absence of a low activation energy reaction path, the 90-120 kcals/mole strain energy calculated for 2b would not preclude the existance of 2b in light of the 101 and 153 kcals/mole strain energy measured for benzvalene and prismane, respectively.

Yamaguchi, *et. al.*,[8] employed the MINDO/3 geometry optimization in a GHF-study of 2 and 3 and predicted ground state singlets for both species. Optimum geometries were not reported for the calculations.

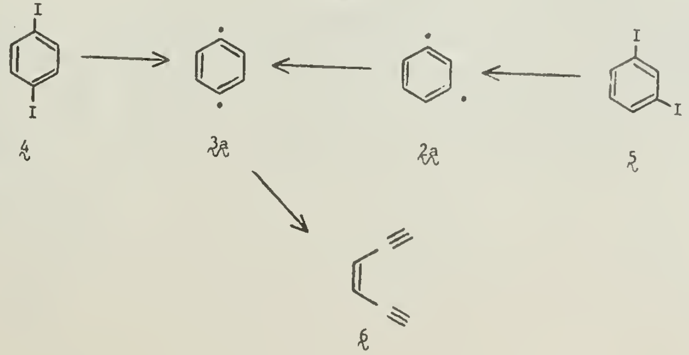
Noell and Newton[9] reported that *ab initio* GVB limited geometry optimization calculations with the 4-31 basis set predicted singlet ground states for 2 and 3 with geometries not appreciably different from benzene. The bicyclic structures were calculated to lie 32 and 38-77 kcals/mole above the biradicals 2a and 3a, respectively.

Thiel[10] reported that a modified MINDO/3 program that included correlation effects (MNDOC) confirmed the prediction of the Dewar MINDO/3 study[6] that 1 and 2 were of similar stability. The MNDOC calculation revealed single energy minima corresponding to biradical structures to be optimum geometries for 2 and 3.

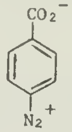
The geometry optimized calculations consistently predict singlet ground states for 2 and 3 yet do not reach a consensus regarding probable geometries and relative energy separations. This result may indicate that bicyclic and biradical structures are of similar energy.

Experimental Investigations. Early attempts to produce 2 and 3 were based on the decomposition of disubstituted benzenes. Fischer and Lossing[11] studied the thermal decomposition of 1,3- and 1,4-diiodobenzenes in a reactor at 960°C and analyzed the products directly by mass spectrometry. 1,4-diiodobenzene (4) produced the cations from iodophenyl radicals, benzene, and a species of m/e 76. The ionization potential of the m/e 76 was found to be 9.40 eV which agreed closely with 9.46 eV predicted for the hexadiynene 6. The diynene 6 was postulated to arise by ring opening of the diradical 3a resulting from loss of two iodine atoms from 4 as outlined in Scheme I. Pyrolysis of the 1,3-diiodobenzene (5) also generated an m/e 76 peak with an ionization potential identical to that obtained in the decomposition of 4. This result was rationalized by rearrangement of 2a to 3a as outlined in Scheme I.

Scheme I



Berry, *et. al.*,[12] studied the flash initiated decomposition of isomeric benzene diazonium carboxylates by time resolved mass spectrometry and flash-absorption optical spectroscopy. The UV absorption spectrum of the gaseous decomposition products from benzene diazonium 4-carboxylate (7) revealed a continuum from 2900 mμ to shorter wavelengths with a possible maximum at 244-246 mμ. The continuum was present from 50 μsec to 0.5 sec after flashing. Two additional transient absorption bands at 328 and 339 mμ appear 200 μsec to 0.5 sec after photolysis but disappear within minutes. The bands and continuum could not be assigned to any previously known compound. The mass spectrum revealed a strong m/e 76 species that persisted for as long as two minutes. The gaseous decomposition products from benzene diazonium 3-carboxylate (8) also exhibit a continuum from 2900 mμ to short wavelengths with bands at 328 and 339 mμ. These bands are visible 45-200 μsec after the flash and are apparently identical to those seen in the decomposition of 7. A strong m/e 76 peak was observed in the mass spectrum having a lifetime of 400-600 μsec. Analysis of the optical absorption spectra and mass fragmentation patterns for the decompostions of 7 and 8 ruled out the diacetylenic structure 6 proposed by Fischer and Lossing.[11] On the basis of the mass fragmentation pattern, the m/e 76 transient from the decomposition of 7 was tentatively assigned structure 3a or alternatively, 3b. Comparison of the fragmentation pattern for the decomposition of 8 with model compounds led the authors to conclude the m/e 76 transient was 1,3-dehydrobenzene and they proposed 2a or 2b as reasonable structures.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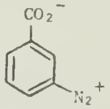
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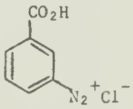
Rossi, *et. al.*, [13] reported isolation of products consistent with the formation of intermediates having structures 2c and 3c from the thermal decomposition of solid carboxybenzene-diazonium salts 9 and 10, respectively, and analogous structures for the nitro analogues 11, 12, and 13, respectively, *in vacuo*. Rossi proposed a stepwise elimination mechanism for the explosive decomposition of salts 9 to 13. Alternative mechanisms involving trapping and decomposition of reactive intermediates exclusive of 2c and 3c could be written to rationalize the products attributed directly to 2c and 3c.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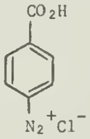
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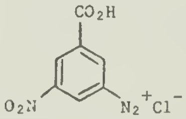
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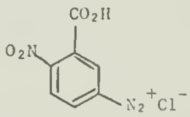
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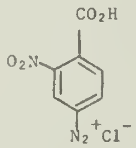
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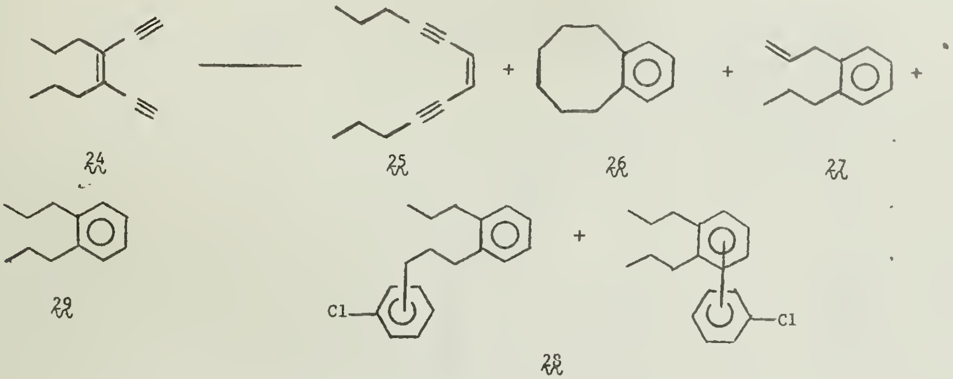
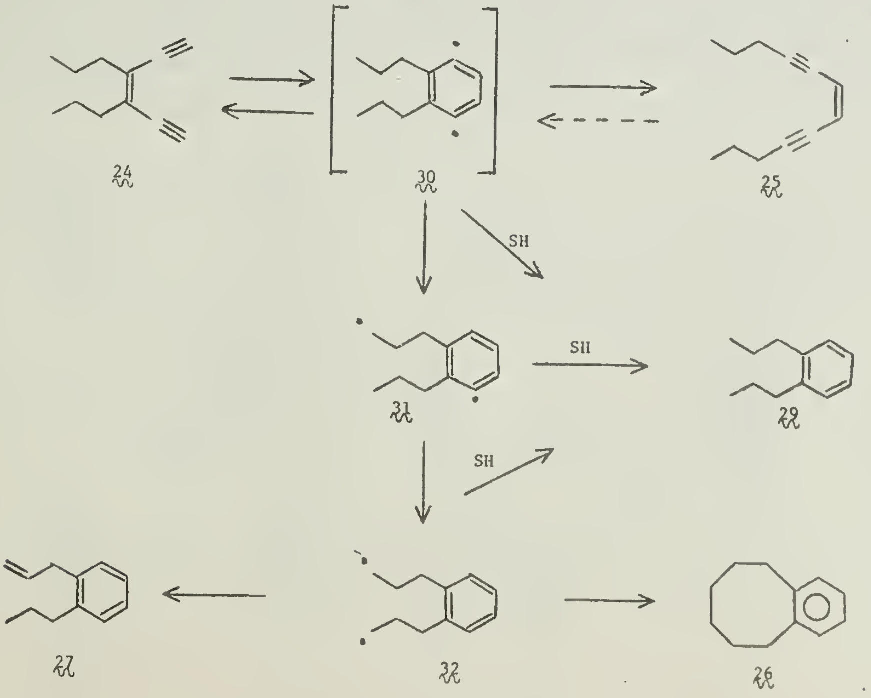
Bergman and co-workers[14] have reported rearrangement and trapping studies of a number of *cis*-hexa-1,5-diyn-3-enes in gas phase and solution pyrolysis which implicate the existence of a biradical having structure 3a. Kinetic and spectroscopic evidence for the intermediacy of 3a was obtained from the solution pyrolysis of the dialkyl substituted diyneme 24. As shown in Scheme II, pyrolysis of the diynene 24 in chlorobenzene at 196°C gave the major products 25, 26, and 27 along with several isomeric dialkylbenzene substitution products 28. The latter compounds were identified as $C_{13}H_{21}Cl$ materials by VPC-MS analysis. First order kinetics were seen for the disappearance of 24 over a 34°C range with $k_{obs} = 6.9 \text{ X } 10^{-4}$ sec^{-1} at 156°C. Addition of 1,4-cyclohexadiene as a hydrogen atom source to the chlorobenzene pyrolysis solution led to the formation of a new product, o-di-n-propylbenzene (29) at the expense of the unimolecular products 25, 26, and 27. Several isomeric C_{18} and C_{12} products were formed and in this case were attributed to aryl/cyclohexadienyl radical combination and dimerization of cyclohexadienyl radicals, respectively. The observed rate of disappearance of 24 was unchanged in the presence of the trap. Pyrolysis of 24 in the presence of 3,3,6,6-tetradeuterio-1,4-cyclohexadiene led to the formation of d_2-29 with 66% d_2-aryl, 33% d_2-alkylaryl, and 1% d_2-alkyl and formation of deuterated C_{18} and C_{12} products. As outlined in Scheme III,

Scheme II



a mechanism consistent with these results would involve initial ring closure of 24 to generate the di-n-propyl-1,4-dehydrobenzene 30, which in the absence of trapping agent could ring open to 25 or undergo intramolecular hydrogen atom transfer to produce biradical 31. Intermediate 31 could suffer a second intramolecular hydrogen transfer to generate 32 which would give products 26 and 27 by intramolecular ring closure and hydrogen atom transfer, respectively. Trapping of the intermediate biradicals 30, 31, and 32 could lead to the formation of 29. The d_4-cyclohexadiene trapping experiment demonstrated 29 came predominantly from biradicals 30 and 31. From kinetic data, Bergman concluded that 30 was a

Scheme III



discrete intermediate having a lifetime of ca. 10^{-9} to 10^{-8} sec at 200°C. This result contrasts sharply with Berry's assignment[12] of a 1,4-dehydrobenzene structure to the long-lived m/e 76 species from the decomposition of 7. Provided the m/e 76 is a 1,4-species, differences must exist in the structure or the electronic state of the two species since no hexadiynene, the relaxation product of 3a, was observed in the decomposition of 7. The reactive spin state of 30 was characterized in chemical trapping studies and CIDNP experiments as a singlet at elevated temperatures.[14e] Results of the thermolysis do not allow conclusions to be drawn regarding the ground state structure of 3. The possibility that a bicyclic ground state may be in equilibrium with the biradical or that the reactivity of 3b may be similar to that expected for the biradical cannot be ruled out. The reaction coordinate diagram in Figure 2 was constructed from calculated activation parameters, estimated rate constants and group additivity estimated heats of formation for the unimolecular reaction steps of Scheme III.

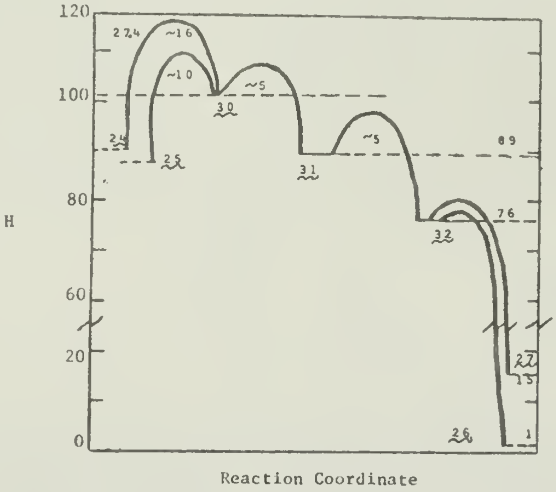
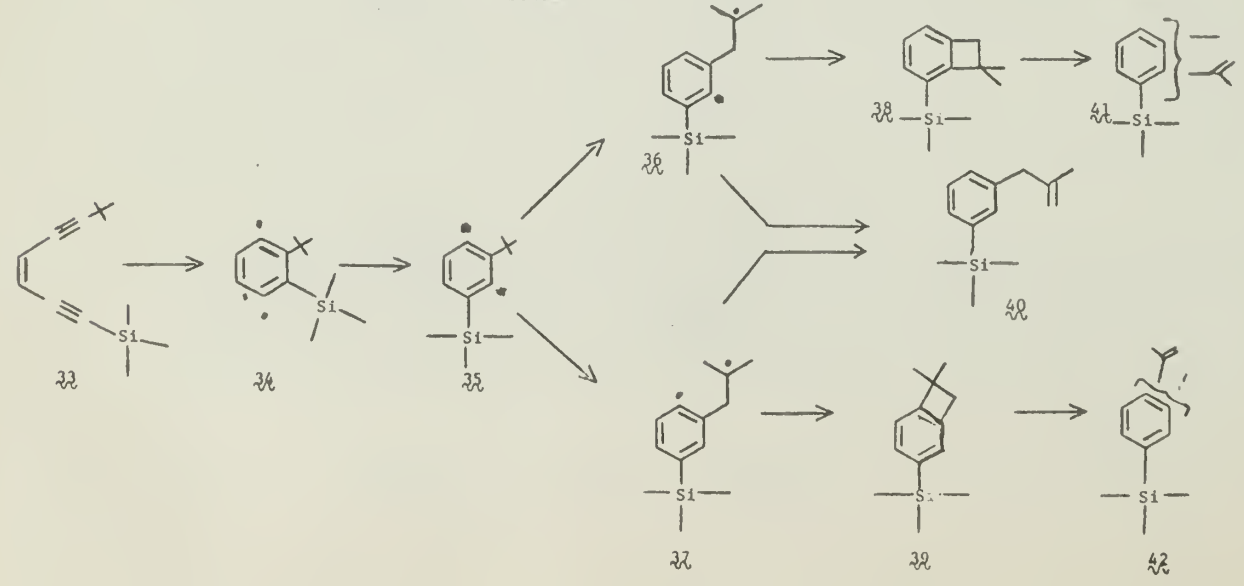


Figure 2. Enthalpy diagram for the reaction of 24 (all units in kilocalories per mole).

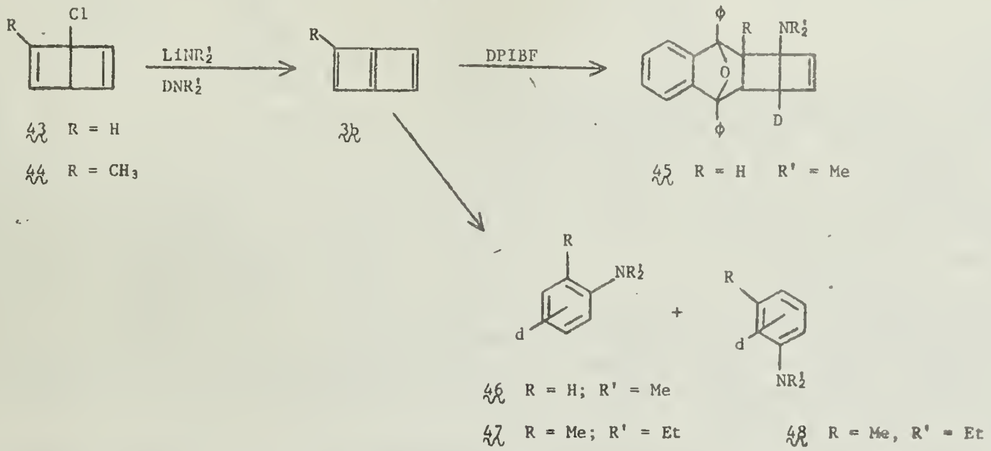
Bergman, et. al.[14b] reported that gas phase pyrolysis of the diethynyl olefin 33 gave products 40, 41, and 42. Compounds 41 and 42 were shown to be single isomers derived from benzocyclobutanes 38 and 39, respectively, by independent synthesis. The mechanism suggested for the formation of the observed products is presented in Scheme IV. Formation of products 41 and 42 is most consistent with a path involving the 1,3-dehydrobenzene 35 which results from 34 by a 1,2-silicon shift.

Scheme VI



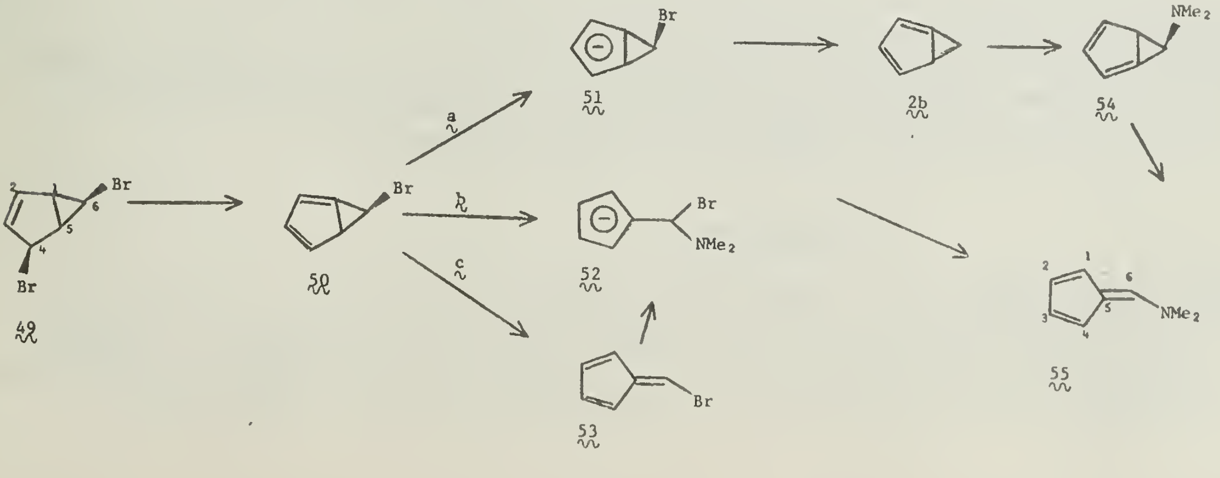
Breslow and co-workers[15] reported that treatment of the chloro Dewar benzene 43 with LiNMe$_2$/DNMe$_2$ in TMEDA/THF at -35°C in the presence of diphenylisobenzofuran (DPIBF) led to the formation of the adduct 45 in 10-15% yield. This result was consistent with generation of 3b as shown in Scheme VII. In the absence of DPIBF, 43 was converted quantitatively to a mixture of d_0 to d_3 anilines 46. Similar treatment of the methylated compound 44 with LiNEt$_2$/DNEt$_2$ at -10° to -15°C produced a mixture of d_0 to d_3 toluidenes 47 and 48 as the major products. Control reactions led Breslow to conclude that conversion of 43 and 44 to the substituted anilines was initiated by base promoted elimination of HCl to generate 3b. Addition of the dialkyl amine across the central double bond of 3b followed by ring opening would give the observed d_1-anilines. The d_0 and d_2-d_3 product formation was rationalized by direct displacement of chloride and H-D exchange on intermediates, respectively. The relative yields and extents of deuteration indicated that the elimination and displacement rates were approximately equal. These results confirm Dewar's prediction that 3a and 3b can exist separately and possess different chemistry.

Scheme VII

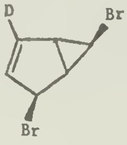


Washburn and co-workers[7,17] reported that treatment of the exo, exo-dibromobicyclohexane 49 with ^{t}BuOK in HNMe$_2$/THF at -75° gave the aminofulvene 55. A priori, the conversion of 49 to 55 could result from two successive HBr eliminations or an HBr elimination followed by substitution of HNMe for bromide as shown in Scheme VIII, path a, and paths b and c, respectively. Initial base induced elimination of HBr from the dibromide 49 would produce 50 which in path a could ionize to 51, then lose bromide to generate 2b. Nucleophilic addition of HNMe$_2$ followed by protonation would produce 54 which could undergo electrocyclic ring opening to the product fulvene 55. Alternatively, fulvene 55 could result from bromide loss from the cyclopentadienide 52. The intermediate anion 52 could be formed from diene 50 by a nucleophilic ring opening reaction as shown in path b or by addition of the amine to bromofulvene 53 which resulted from the allowed ring opening of the bromodiene 50.

Scheme VIII



In order to determine which of the three paths were operative, the reactions of specifically deuterated and ^{13}C-enriched 49 were investigated. Reaction of a 1:1 mixture of the 2-d_1-56 and 4-d_1-57 compounds resulted in a mixture of aminofulvenes deuterated at C_1 and C_4. Reaction of 2- and 4-^{13}C enriched 58 and 59, respectively, produced aminofulenes in which the ^{13}C-label was distributed equally between C_1, C_4 and C_2, C_3. If the transformation of the labeled dibromide mixture to the fulvene had occurred by path b or c, deuteria would be located at C_2 and C_3 only and ^{13}C-enrichment at C_2 and C_3 only. Since these results were not realized, paths b and c of Scheme VIII were ruled out. To be consistent with the observed labeling, intermediate d_1-2b of path a must undergo a trans nucleophilic addition at C_6 and electrophilic addition at C_2 followed by a 1,5-sigmatropic shift of the C_2-hydrogen syn to the NMe_2 group of 60 to generate d_1-54 as shown in Scheme IX. Electrocyclic ring opening of d_1-54 would produce the d_1-55 product with the observed labeling. The path outlined in Scheme IX would predict ^{13}C-labeling at C_1, C_3 or C_2, C_4 for compounds 58 and 59, respectively, which was not observed. This difference between the predicted and observed ^{13}C-enrichment was resolved in a study of the 2-Bu^t dibromide 61 which revealed that the C_1,C_4 and C_2, C_3 carbons were interchanged by a nucleophilic addition-elimination reaction that destroyed the sterochemistry about the double bond generated by the electrocyclic ring opening to produce the fulvene. The results of this study suggest that 1,3-dehydrobenzene may be a misnomer in that 2 is more accurately described as bicyclo[3,1,0]-hexa-1,3,5-triene (2b) in these reactions.



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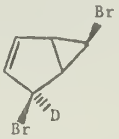

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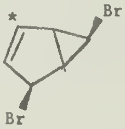

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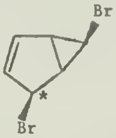

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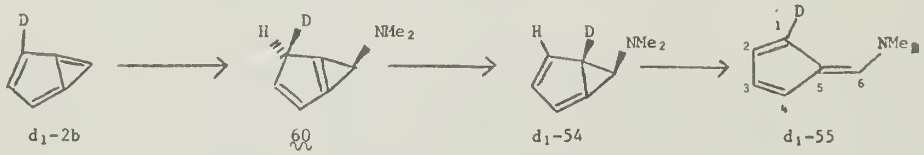
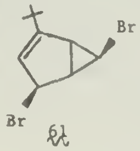
Scheme IX





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Conclusion. There is experimental evidence that 1,3- and 1,4-dehydrobenzenes have been generated by pyrolysis of substituted diethynyl olefins and by dehydrohalogenation of suitable bicyclic precursors. In accord with theory, these species were found to be highly reactive intermediates.

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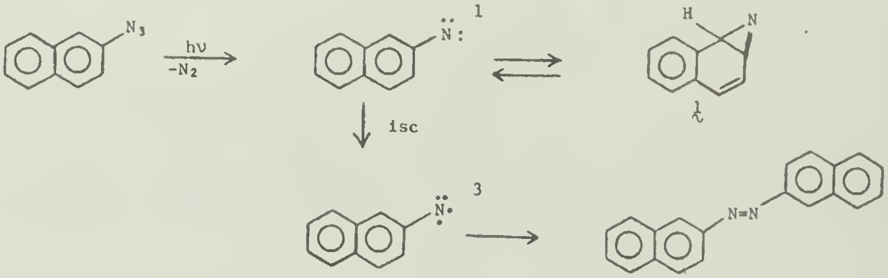
MECHANISMS IN ARYL AZIDE PHOTODECOMPOSITION

Reported by Alan Schrock February 11, 1982

The mechanisms for the formation and reactions of intermediates in aryl azide photochemistry have been a subject of interest for many years.[1] Photolysis of aryl azides generates nitrenes which undergo reactions characteristic of their spin state. The higher energy singlet aryl nitrene may undergo an intramolecular aromatic C-C bond insertion first postulated by Huisgen,[2] and later supported by the work of Sundberg,[3] Chapman[4] and Dunkin,[5] which gives an azirine, 1. The azirine is suggested to be in equilibrium with the singlet nitrene. The lower energy triplet aryl nitrene obtained by intersystem crossing from the singlet nitrene is stable in a low temperature matrix but decays to the azoarene upon melting.[6] An example of these processes is shown in Scheme I.

Scheme I

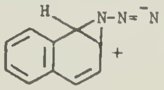


The azirine has been invoked to explain the products found when nucleophiles are present during irradiation of the aryl azides. When β-azido anthracene is irradiated in dimethylamine, the product isolated is 1-amino-2-dimethylamino-anthracene in greater than 75% yield.[7]

However, the azirine mechanism fails to explain the great difference in reactivity of α- and β- aryl azides. For example, high yields of trapped products are obtained with β-azidonaphthalene and β-azidoanthracene with thiols, alkoxides, mono-, di-, and tri-substituted amines as nucleophiles, while yields typically less than 10% are found with the α- azides.[8]

We have found that when 1,1-dimethyl hydrazine (DMH) is the nucleophile, β-azidonaphthalene gives the expected 1-amino-2-(2,2-dimethylhydrazinyl) naphthalene, while α- azidonaphthalene gives 1-aminonaphthalene in 95% yield. We have generalized this reactivity pattern in aryl azides which have singlet nitrenes that can be monitored by transient absorption spectroscopy. The products from 1-azidopyrene and β-azidoanthracene are 1-aminopyrene and 1-amino-2-(2,2-dimethylhydrazinyl) anthracene respectively. In both cases, the reactions occur with precursers to the singlet nitrenes.

The amines resulting from the α-azides are most likely the result of electron transfer quenching of the singlet excited state of the azide. We propose a new intermediate, 2, a precurser to the singlet nitrene, to explain the reactivity of the β-azides, with the naphthyl system as an example.

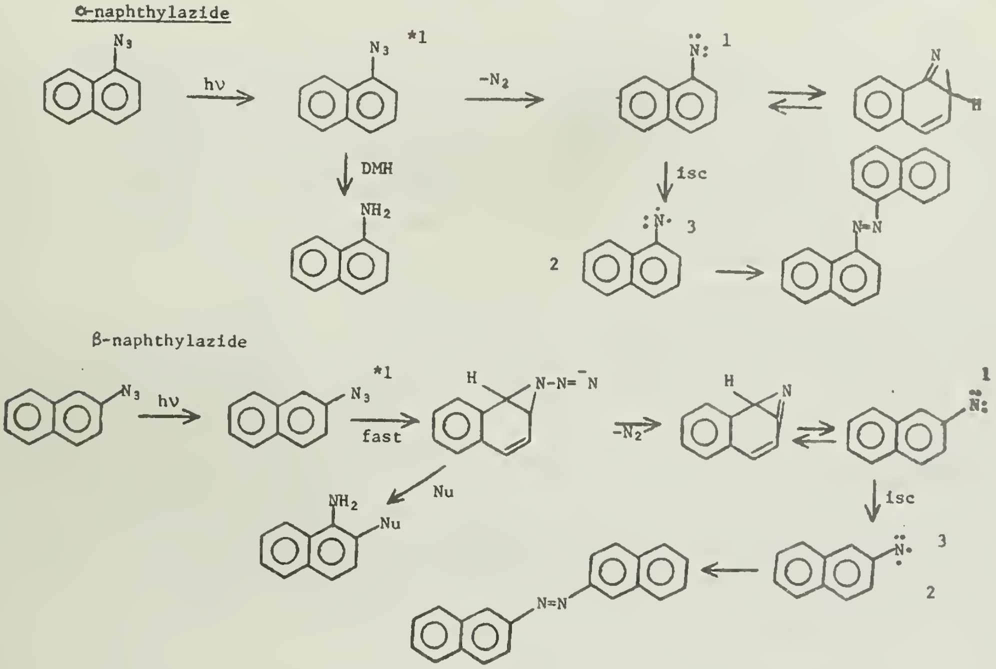


2

It has previously been proposed that the azoarenes are products of either triplet nitrene-azide reactions[9] or triplet nitrene dimerizations.[10] We have conclusive evidence that triplet nitrene dimerization is the mechanism for formation of the azoarenes. The rates of formation of the azoarenes fit second order rate laws with rate constants on the order of 1 X $10^{9}m^{-1}s^{-1}$. The addition of phenyl azide has no effect on the rates of product composition. A laser power dependence is observed for the rate of formation of the azoarenes.

Our results are summarized in Scheme II using the naphthyl azides as models.

Scheme II



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FAST ATOM BOMBARDMENT; A NEW IONIZATION TECHNIQUE FOR MASS SPECTROMETRY

Reported by Doug Phillipson February 15, 1982

Fast atom bombardment (FAB) is a new ionization technique which is becoming a powerful adjunct to other common ionization techniques currently employed by the organic and inorganic mass spectrometrist. FAB is especially suited to the analysis of polar, thermally labile, non-volatile and/or high molecular weight molecules. There are a number of other ionization techniques which have attempted to alleviate the difficulties associated with these problem molecules.[1,2] Chief among these other techniques is field desorption (FD). Field desorption mass spectrometry is practiced routinely in a number of labs but it is not without its drawbacks. It is a difficult technique to master, and at best produces weak ion beams making high resolution mass measurements very difficult. Another disadvantage of FD is that the spectra obtained usually contain only a peak or cluster related to the molecular ion, with little if any fragmentation observed.[3] Fast atom bombardment is an easier technique by comparison. FAB sources produce long-lasting and relatively intense ion beams for a majority of the compounds studied. The spectra usually contain structurally significant fragment ions as well.

The technique of FAB is a refinement and outgrowth of secondary ion mass spectrometry, which although primarily used by analytical chemists and others for surface analysis, has been used to generate gas phase ions of organic compounds.[4,5,6] In FAB a sample is mixed with a small amount of glycerol, or other matrix medium, on a stage or target which is then inserted into a slightly modified field desorption ion source. A neutral beam of argon or xenon atoms, accelerated to 2-8 KeV by an atom gun, strike the target causing some of the sample molecules to become gas phase ions. The ionized sample molecules are then accelerated, focused and analysed in the usual manner.

Mass spectrometers fitted with FAB sources have provided useful spectra for quite a few diverse compound types. These include some important classes of biomolecules, such as underivatized peptides[3,7,8,9,10] nucleosides and other organic salts,[11]zwitterionic polyene antibiotics,[12]glycoside antibiotics[13,14] and colbalamines[15]

The mechanism of the ionization process is unknown. The spectra obtained from a FAB source resemble those from plasma desorption or chemical ionization sources. In light of this, Barber et. al.[13] postulate that as the energetic atoms strike the target, local pockets of a dense plasma made up of sample and glycerol (or other non-volatile solvent) are formed. Some molecules may give [H+] or other Bronsted or Lewis acids which could in turn protonate or sodiate neutral molecules, yielding the ions which are eventually detected. Another possibility is that ionization takes place in the sample matrix and pre-formed ions are sputtered into the gas phase by momentum transfer from the high energy atoms.

In two or three years FAB has developed from a curious offshoot of secondary ion mass spectrometry to a fully commercial technique for mass spectrometry. The rapid acceptance of the technique is due to its simplicity of operation and the dramatic successes achieved in contributing to the structure elucidation of unknown compounds. In addition FAB produces spectra of compounds not amenable to analysis by mass spectrometry using other ionization techniques. Although the energy inhomogeneity of the beam is significant, high resolution mass measurements employing FAB have been successfully carried out.[16] Future work will be directed toward determining the ionization mechanism and reducing the energy inhomogeneity of the ion beam as it leaves the target surface.

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ASPECTS OF THE PHOTOREDUCTION OF BENZOPHENONE BY AMINES

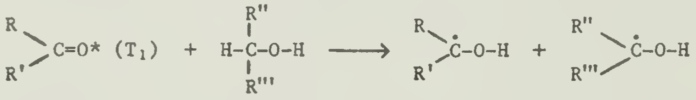
Reported by Judith E. Porter February 22, 1982

Introduction. The reduction of photoexcited carbonyl compounds by alcohols and amines has been studied for many years. As early as 1900 it was known that certain carbonyl compounds were reduced by alcohols and that useful yields of hydrols and pinacols could be obtained.[1,2] The reduction by alcohols, however, is not of general usefulness. The types of carbonyls which are efficiently reduced are limited.[3]

Initially the mechanism for photoreduction by amines was assumed to be the same as that by alcohols.[4,5] As the amine systems were studied in more detail, reactivity differences were noticed and it became evident that although the mechanisms for the two systems were similar, they were not the same.[6] In 1968 Cohen and co-workers[7] proposed the charge transfer mechanism for photoreduction by amines which received general acceptance by the early 1970's.[6] Only in the last two years have experimental observations been made that require a modification of the mechanism.

The Mechanism. As amine photoreductive activity began to be compared to that of alcohols, differences in the types of carbonyls reduced by the two systems became apparent. Alcohols were found to be efficient reducing agents for ketones possessing a low-lying n,π* reactive triplet state while ketones with low-lying π,π* or charge transfer triplet states were not photoreduced efficiently (examples of the latter are fluorenone, xanthone, aminobenzophenones, α- and β-naphthyl carbonyls).[6b] However, amines were found to not only photoreduce n,π* reactive triplet states (although not always as efficiently as alcohols) but also π,π* and charge transfer triplet states under the right conditions.[6] The amine must have an α-hydrogen for efficient photoreduction. This is also a necessary criterion for efficient reduction by alcohols.

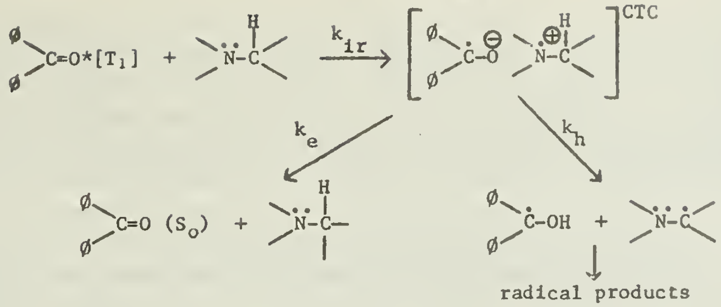
In the photoreduction of ketones by alcohols the excited triplet ketone abstracts a hydrogen atom from a carbon α to the hydroxyl group forming a pair of hydroxymethyl radicals (eqn. 1).[8] The abstraction is thought to be assisted by electron donation from oxygen which results in a polar contribution to the



$$\mathrm{RR'C{=}O^{*}\,(T_1)} + \mathrm{H{-}C(R'')(R''')\!-\!O{-}H} \longrightarrow \mathrm{RR'\dot{C}{-}O{-}H} + \mathrm{R''R'''\dot{C}{-}O{-}H} \qquad (1)$$

transition state.[9] It was believed that amines would show the same reactivity.[10] Although the net result in the amine reaction is similar, this reaction is now generally accepted to proceed by formation of a charge transfer complex, k_{ir}, through interaction of the excited triplet ketone with the nonbonding electrons of the nitrogen.[6,7,9b] There has been some discussion in the literature about the exact nature of this complex and some hesitation has existed about regarding it as electron transfer.[6b,7,9a,11] (Even though there has been extensive study in the area of electron transfer complexes as intermediates in organic photoreactions,[12,13] it has only been in the last year that the direct proof has been obtained to show that the initial reaction in this case is electron transfer and not charge transfer.)[14] Once the complex has been formed there can be α-hydrogen transfer, k_h, which leads to radicals, or spin inversion may occur with quenching, k_e (Scheme I). The quantum yield of reduction, $\Phi_{\text{reduction}}$, is then determined by the fraction $f = \frac{k_h}{k_e + k_h}$. The initial charge transfer interaction will lower

Scheme I



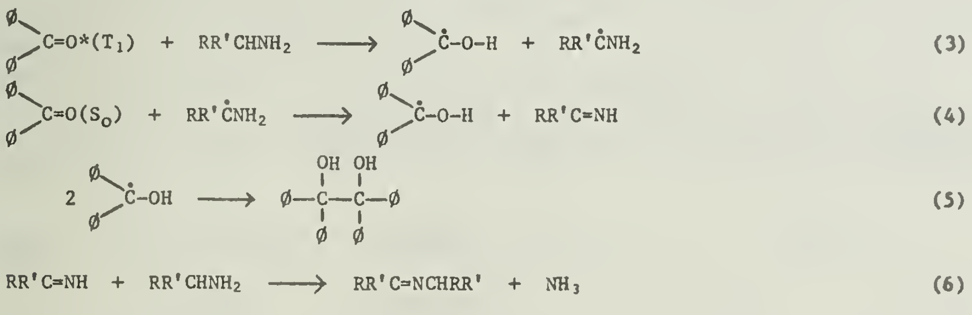
the barrier to hydrogen abstraction but also open a path to a quenching reaction which can reduce the maximum $\Phi_{reduction}$ of two.[6,23] The values for k_{ir} are predicted to be high due to the insensitivity of the system to physical quenchers and amine concentration.[11f] Therefore, quantum yields for reduction would be dependent on intersystem crossing rates and the relative magnitudes of k_e and k_h.

Development of the Mechanism. The early work in amine photoreductive systems was largely based on synthetic utility. The most useful products and highest yields were found with reactions carried out in inert solvents without excess amine. Greater than 85% yields of pinacols could be obtained with >90% conversion of amines to imines.[4] Upon hydrolysis of the imines good yields of carbonyl compounds were obtained (eqn. 2).[10] Scheme II outlines the overall reaction for

$$RR'CHNHR'' \longrightarrow RR'C{=}NR'' \longrightarrow RR'C{=}O + H_2NR'' \qquad (2)$$

primary and secondary amines.[6a] The observed results point to one hydrogen being transferred to excited triplet ketone (eqn. 3) forming an amine derived radical and then this radical transfers a second hydrogen to a ground state ketone molecule (eqn. 4). This allows for the theoretical maximum quantum yield of two for these systems.[10]

Scheme II



When photoreductions were carried out in excess optically active amine, recovered amine showed no racemization indicating that transfer of hydrogen from the α-carbon is not reversible (or the complex formed from hydrogen transfer is not free to rotate in the cage) and therefore quenching (leading to $\Phi_{reduction}$ <2) can not occur in this fashion. Information about the initial hydrogen abstraction was gained with deuterated amines.[10] Amines which contained N-D showed very small (≤10%) inverse isotope effects while amines with α-deuterium substitutions showed an isotope effect $k_H/k_D \sim 1.6$. These results suggest that abstraction of the amine's α-hydrogen is involved in the rate-determining step of the reaction. However, the isotope effect for α-deuterium is much less (∿1/2) than that observed for α-deuterium effects in photoreduction by alcohols.

The lower than maximum quantum yield is then explained by back charge transfer from the initial complex.[10] Once the complex has formed, quenching can occur via reverse charge transfer. This type of quenching action is the same as that proposed for many types of electron donors.[15] The later stages of the reaction have been shown to proceed via normal free radical combination reactions by competition and inhibition effects by mercaptans.[16]

The charge transfer interaction was supported by the results of quenching experiments. Photoreduction of benzophenone by amines was less sensitive to quencher concentration than reduction by alcohols.[11b] The charge transfer complex would reduce the concentration of free triplet ketone available for quenching interaction. This process predicts that amines containing no transferable hydrogens should act as quenchers only. This is consistent with observed fact.[11b,17,19] Overall, this mechanism accounts for the fact that amines act as both quenchers and hydrogen donors and also the differences observed between the photoreductive reactivity of amines versus alcohols. Additional support for the charge transfer interaction was gained by studies relating the ionization potential of amines with predicted k_{ir}'s. As expected for this type of interaction, ionization potentials generally decrease with increasing reactivity.[18,22,27] Also, it has been found that electron withdrawing groups on the amine slightly decrease k_{ir} while electron releasing groups enhance k_{ir}.[18a,23]

Support for the existence of electron transfer instead of charge transfer in these systems was obtained by the observation of radical ions by flash photolysis in particular cases.[11b,g,21,28] The formation of ions was found to be solvent dependent.[11g,h] As the polarity of the solvent used increased, the yield of ions also increased. This dependence of radical ion yield on solvent polarity was considered to be good evidence for the occurrence of electron transfer since this same solvent effect has been observed in other systems where electron transfer is believed to occur.[11g,19b,20] As mentioned above, it was not until 1981 that direct evidence was obtained to support electron transfer over charge transfer in the photoreduction of benzophenone.

Estimates of k_{ir} values have been based on diffusion controlled quenching experiments according to the Stern-Volmer equation. Some of the results are given in Table I.

Table I

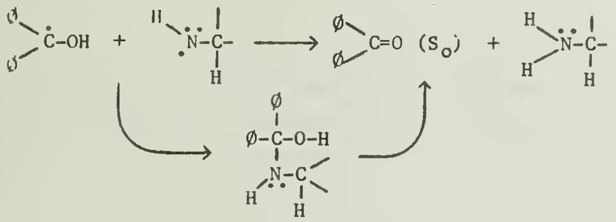
Estimates of k_{ir} Based on Quenching Studies

Ketone	Amine	Solvent	k_{ir} ($M^{-1}s^{-1}$)	Ref
Benzophenone	2-butyl	benzene	$5x10^{7}$	7
Benzophenone	t-butyl	benzene	$1.9x10^{8}$	18a
Benzophenone	N-methyl-2-butyl	benzene	$1.4x10^{9}$	18a
Benzophenone	p-cyanodimethylaniline	benzene	$2.0x10^{9}$	18a
Benzophenone	dimethylaniline	benzene	$2.7x10^{9}$	18a
Benzophenone	p-methyldimethylaniline	benzene	$4.3x10^{9}$	18a
Benzophenone	triethyl	benzene	$2.3x10^{9}$	18a
Benzophenone	triethyl	benzene	$2.5x10^{9}$	42
Benzophenone	triethyl	CH_3CN	$3.8x10^{9}$	42
Benzophenone	1-azabicyclo[2.2.2]octane	benzene	$1.8x10^{8}$	42
Benzophenone	1-azabicyclo[2.2.2]octane	CH_3CN	$2.2x10^{9}$	42
Benzophenone	1,4-diazabicyclo[2.2.2]octane	benzene	$2.4x10^{9}$	42
Benzophenone	1,4-diazabicyclo[2.2.2]octane	CH_3CN	$11x10^{9}$	42

Nanosecond Flash Photolysis Results. In 1980, Cohen and coworkers[24] were able to measure the quantum yield of hydroxymethyl radical, $\Phi_{radical}$, from the reaction of triplet benzophenone (BZ) with aliphatic amines in benzene using a flash laser photolysis apparatus. They observed that the $\Phi_{radical}$ ranged from 0.9 to 1.0 in all systems studied. Since the hydroxymethyl (HM) radical is believed to be the product of hydrogen abstraction after the initial formation of the charge transfer complex (CTC), the proposed back charge transfer quenching process from the CTC was not occurring in this system. This result required a modification of the accepted mechanism.

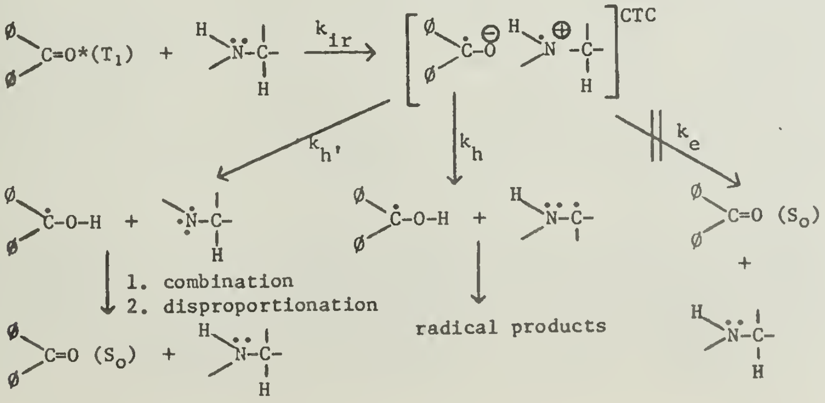
Experimental findings indicated that hydrogen was abstracted efficiently from both the N-H and α-C-H positions as the $\Phi_{radical}$ was $\sim$1.0 for t-butylamine as well as triethylamine.[24] However, $\Phi_{reduction}$ was very low in the absence of α-C-H. Hydrazine, which can only react via N-centered radicals, is a very inefficient photoreducing agent for benzophenone.[23,29] These results were explained by making modifications in the original mechanism shown in Scheme I.

The proposed back charge transfer quenching from the CTC, k_e, does not occur to any appreciable extent and essentially all CTC goes on to form radicals. In the case of amines with both N-H and α-C-H, two sets of radicals can be formed. Abstraction of α-C-H gives HM plus α-aminoalkyl radicals, k_h, while abstraction of N-H results in HM plus alkylaminyl radicals, $k_{h'}$. The low $\Phi_{reduction}$ found for amines lacking α-C-H requires that the HM/alkylaminyl radical pair disproportionate to ground state ketone and amine. This may occur by direct hydrogen abstraction or by initial combination of the radicals then disproportionation (eqn. 7). The latter has been proposed to explain the observed results in thiyl,[25] anilino,[26] and hydrazyl[23] radical systems. No evidence was found for disproportionation of C-centered radicals. When reductions were carried out in optically active 2-aminobutane, recovered amine showed no racemization.[30] The low $\Phi_{reduction}$ for tertiary amines is attributed in part to inefficiency of C-centered radicals in reducing ground state ketone. The resulting modified mechanism is given in Scheme III.



(7)

Scheme III



The results of Cohen's photolyses are given in Table II. The $\Phi_{radical}$ in all cases (except with DABCO) is >.9, but the $\Phi_{reduction}$ varies greatly with the nature of the amine. t-Butylamine gives an extremely low $\Phi_{reduction}$ indicating the importance of α-hydrogen for efficient reduction. The secondary amine gives a lower $\Phi_{reduction}$ than primary amines. This is attributed to the weaker bond energy of secondary N-H versus primary N-H (96 vs 103 kcal/mol). This would be expected to lead to a larger amount of N-centered radical with a secondary amine and therefore lower $\Phi_{reduction}$. The apparent inefficient reduction by the tertiary amine can be attributed to several factors. First, in non-polar solvents the reduction by tertiary amines is accompanied by light-absorbing transients that complicate quantum yield determinations.[6b,7,30] The transients also appear to be efficient quenchers of triplet BZ. Secondly, reduction in the rate of the oxidation of ground state ketone by tertiary-amine-derived radical as opposed to primary- or secondary-amine-derived radical would also lower $\Phi_{reduction}$.[32] The enamine (of DABCO) formed in such a process is not stabilized by conjugation so the HM/aminoalkyl radical pair would live longer and disproportionation of C-centered radicals might become important.

Table II

Benzophenone Nanosecond Flash Photolysis Results

Amine	k_{ir} $(M^{-1}s^{-1})^a$	$\Phi_{radical}$	$\Phi_{reduction}$
t-$C_4H_9NH_2$	6.4×10^7	.96	.06
sec-$C_4H_9NH_2$	2.3×10^8	1.00	.54
c-$C_6H_{11}NH_2$	3.3×10^8	.95	.49
n-$(C_3H_7)_2NH$	3.4×10^9	.90	.34
$(C_2H_5)_3N$	3.0×10^9	1.00	.3
DABCO	4.5×10^9	.73	.09

$^a k_{ir}$ determined by triplet decay dependence on amine concentration.

The quantum yields of radical and reduction products are lower for 1,4-diazabicyclo[2.2.2]octane (DABCO) even though the charge transfer rate appears to be high. The high stability of the DABCO radical cation[33] and the strained nature of the α-C-centered radical have been used to explain the low quantum yields. It is likely in this system that back charge transfer, k_e, becomes important.

Picosecond Flash Laser Photolysis Results. Recently Peters and co-workers have been able to observe the dynamics of the photoreduction of BZ and fluorenone (Fl) by DABCO by utilizing picosecond absorption spectroscopy.[34] They were able to directly observe the formation of the radical anions of the ketones. This is the strongest evidence to date for the existence of electron transfer versus charge transfer in this system. The experiments were performed using 1M amine which places an amine molecule in the first solvent sphere of greater than 80% of the ketone molecules. At this concentration, the measured rate constants should not reflect translational diffusion but only rotational diffusion and solvent reorganization.

Using the solvent reorganization model Nagakura and co-workers[35] predicted the half-life for electron transfer to be 16 picoseconds (ps) for BZ/DABCO and 14ps for Fl/DABCO in acetonitrile. Peters found the half-life for both systems to be 20±10ps,[34] in good agreement with Nagakura's prediction.

The BZ and Fl radical anions were found to decay at very different rates. The BZ radical anion persisted beyond 2 nanoseconds (ns) without significant decay in the absorption while the Fl radical anion decayed within 60±20ps. The difference in the stability of the two radical anions can be accounted for by the spin states of the two systems.[36] The Fl radical anion results from electron transfer to the first excited singlet state producing a singlet ion pair while the ion pair produced in the BZ system is a triplet.[34] The BZ radical anion is thus longer-lived in respect to back electron transfer than the Fl radical anion since this process would be spin-forbidden in the former and spin-allowed in the latter.

Further studies on a BZ/triethylamine system gave similar results.[37] The radical anion of BZ was observed with a half-life of 10±5ps and decayed as the HM radical was seen to grow in with a half life of 15±5ps. The HM radical was stable beyond 2ns. Peters also observed a $\Phi_{radical}$ of 1.0 in excellent agreement with Cohen's observations that significant quenching within the CTC, k_e, does not occur in this system.[24] Peters results are summarized in Table III.

Table III

Rate Constants for Electron Transfer

Ketone	Amine	k_{ir} ($M^{-1}s^{-1}$)	Ref
BZ	DABCO	$5x10^{10}$	34
Fl	DABCO	$5x10^{10}$	34
BZ	Et_3N	$11x10^{10}$	37
BZ	Dimethylaniline	$3.6x10^{10}$	14
BZ	Diethylaniline	$4.2x10^{10}$	14

It was previously noted that solvent polarity affects the formation of radical ions from electron transfer.[11g,h] Since the picosecond resolution achieved by Peters allowed the direct monitorization of the yields of radicals and radical anions, a series of studies were initiated to look at the solvent dependence of the formation of these species.[14] It was found that as the dielectric constant decreased, the yield of HM radical versus ketyl radical anion increased (Table IV).

Table IV

Dependence of K_{eq}[a] on Solvent

Solvent	K_{eq} (DMA)[b]	K_{eq} (DEA)[c]	ε
acetonitrile	2.7	0.1	34.5
propionitrile	5.4	0.7	27.8
butyronitrile	7.3	1.7	23.2

[a] $K_{eq} = \frac{\text{HM radical}}{\text{radical anion}}$

[b] dimethylaniline

[c] diethylaniline

Peters observed a blue shift in λ_{max} of the radical ions prior to proton transfer. This shift has been previously noted for the formation of contact ion pairs (CIP) from solvent-separated ion pairs (SSIP).[38] The formation of a SSIP as the initial result of the electron transfer is reasonable based on Weller's[39] observation that electrons can be transferred over an average encounter distance of 7Å. There is ample room for a solvent molecule to be situated between the reactive sites. This would require that the electron be transferred from an amine not directly involved in solvating the ketone.[14] Thus, diffusion to form a CIP would be likely to affect the dynamics of proton transfer. Also consistent with the formation of a CIP was the observation that 2ns after photolysis, there was no dependence on the dielectric constant of the solvent of λ_{max} for the BZ radical anion. There was no detection of any HM radical prior to formation of the CIP in the reduction of BZ by 1M diethylaniline (DEA) and 1M dimethylaniline (DMA). This result is consistent with the increased formation of HM radical as solvent dielectric decreases since with high dielectric solvents the SSIP would be favored while the CIP would be favored with low dielectric solvents.

In 1975 Cohen and co-workers observed a non-first order dependence of $\Phi_{reduction}$ on amine at very high amine concentrations.[40] They attributed this effect to an amine-mediated hydrogen transfer in the CTC. Peters observed an expected increase in rate of electron transfer at high amine concentration but in contrast to Cohen's proposal he observed a decrease in the rate of proton transfer.[14] With an increase from 1.0M to 5.0M amine the proton transfer rate decreased by a factor of four. The rate of CIP formation also decreased by the same factor. Peters has explained this result as follows. At high amine concentration almost every other molecule in the solvent sphere is an amine. Once the electron transfer has occurred, there are amine molecules close enough to the amine radical cation to act as stabilizing agents for the cation. This will decrease the rate of diffusion to form the CIP and hence the proton transfer rate.

Further investigations into solvent effects lead Peters to observe a hydrogen bonding effect on k_{ir} in BZ reduction by DABCO.[14] Increasing the concentration of ethanol in an ethanol/acetonitrile solvent system decreased k_{ir}. Furthermore, this effect was not seen using DEA as the reducing agent instead of DABCO. Peters thus suggested the formation of a hydrogen bond between ethanol and ground state amine. This should decrease k_{ir} since the hydrogen bond would have to be broken before the electron transfer could take place. The absence of the effect with DEA is accounted for by the fact that DEA is a much weaker base than DABCO and forms weaker hydrogen bonds. Studies on the effect of DABCO concentration on the hydrogen bonded carbonyl stretching frequency of BZ showed a decrease in hydrogen bonded ketone with an increase in DABCO concentration; consistent with an increase in the formation of hydrogen bonded amine.

Finally, Peters observed that in the same solvent system, DABCO produced an equilibrium between SSIP and CIP favoring CIP more than the same equilibrium in DEA.[41] This is accounted for by the increased localization of charge in the DABCO radical cation relative to the DEA radical cation thus favoring a strong CIP in the DABCO system.

Summary. The recent developments in nanosecond and picosecond spectroscopy have provided a direct pathway for looking at the individual steps of amine photoreductions of benzophenone. This has been extremely helpful in understanding the dynamics of the individual steps of the reaction and aided in determining the importance of the intermediates. Further work in this field will be helpful in extending this understanding to other systems.

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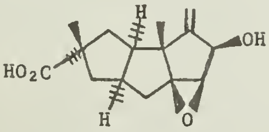
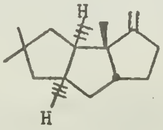
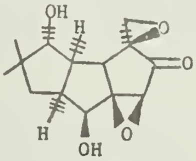
SYNTHESIS OF HIRSUTANES

Reported by Dee Ann Casteel February 25, 1982

In 1947, an extract from the fungus *Stereum hirsutum* was found to exhibit antibacterial properties[1]. Several sesquiterpene metabolites, both active and inactive were isolated at that time. Twenty years later the structure of the major component, hirsutic acid, was elucidated[2] and interest in the hirsutane family of compunds began.[3] The promising antibacterial and antitumor properties, especially of the coriolins,[4,5] as well as the interesting carbon framework[6] have been incentives for the recent synthetic efforts.


hirsutic acid


hirsutene


coriolin

Several synthetic routes to the *cis*, *anti*, *cis*-tricyclo $[6.3.0.0^{26}]$ undecane systems have been established.[7] Lansbury used the successive annelation approach in his early attempts to synthesize hirsutic acid.[8] While these syntheses suffered from lack of stereoselectivity, substantial insight was gained on the steric requirements of the *cis*, *anti*, *cis*- configuration.[9] In 1974, a group of Japanese workers reported the first total synthesis of racemic hirsutic acid.[10] Annelation of the third ring onto a bicyclooctane precursor provided the carbon framework which was then elaborated to the acid. The stereochemistry at C-11 remained a problem which required the separation of isomers at an early step. More recently Trost and co-workers offered a creative approach to the syntheses of hirsutic acid.[11] Using a bicyclic template to set the stereochemistry of four of seven chiral centers, they were able to unravel the polycycle to reveal the hirsutane skeleton. The pre-set stereocenters ultimately controlled the remaining three.

Hirsutene, the parent hydrocarbon, was isolated as a natural product and then synthesized in 1976 starting with a bicyclooctanone.[12] Several types of rearrangements have also been used to make hirsutene. Basic treatment of a linearly fused 6-4-5 tricyclic diol afforded the necessary 5-5-5 system.[13] Alternatively, a bicyclohexanone was allowed to stereoselectively rearrange giving the appropriate skeleton.[14] In another syntheses of hirsutene, Matsumo, *et*. *al*., exploited the proposed biosynthetic pathway to the hirsutanes[15] in their synthetic designs. A triple skeletal rearrangement of protoilludene, a biogenic precursor, allowed access to the requisite framework.

An iterative three-carbon annelation has been reported by Greene in his synthesis of hirsutene.[17] Cycloaddition of a cyclopentene with a chloroketene followed by ring expansion with diazomethane gives the second ring. Reduction and dehydrohalogenation allow a repetition of steps to form the third ring. Diyl trapping reactions have been utilized by Little and co-workers to form linearly fused tricyclopentanoids.[18] Intramolecular trapping gave, in one step, all three rings with four asymmetric centers properly situated for elaboration into the natural systems. The diyl was formed by thermal decomposition of an azo compound.

Finally, two syntheses of coriolin have been published recently, one beginning with cyclooctadiene,[19] and the other proceeding by successive annelation and elaboration.[20]

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TRICARBONYL (DIENE) IRON COMPLEXES IN ORGANIC SYNTHESIS

Reported by Raju Mohan

March 4, 1982

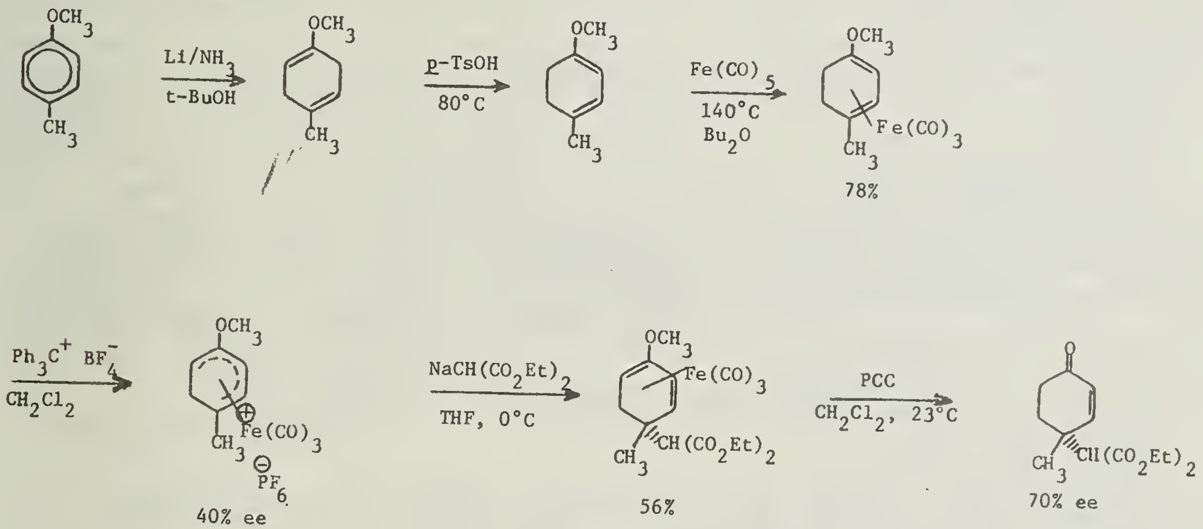
Organometallic complexes involving transition metals have found considerable use in organic synthesis. The metal atom and associated complexes can bring reacting centers into proximity, lower activation energy barriers, enhance substrate reactivity and stabilize high energy products.[1] This review discusses some applications of tricarbonyl (diene) iron complexes in organic synthesis.

Much of the reactivity of these complexes, including the electrophilic[2] and electrocyclic reactions[3] of the dienes, can be rationalized based on simple Frontier Molecular Orbital (FMO) considerations.[4]

Diene complexes can be prepared from iron carbonyl compounds.[5-7] The $Fe(CO)_3$ group can be removed with oxidizing agents such as trimethylamine-N-oxide or ceric salts.[8]

Hydride abstraction from tricarbonyl(diene)iron complexes bearing allylic hydrogens leads to the formation of tricarbonyl(dienyl)iron salts[9] with the yields being dependent on both steric and electronic factors.[10] Some of the more useful applications of these complexes have been the reactions of substituted cyclohexadienyl complexes obtained from metal-ammonia reductions of aromatic compounds.[11] Scheme I illustrates one such example.

Scheme I



Nucleophiles react regiospecifically with cyclohexadienyl complexes to form new C-X bonds, (X=O,S,N,P,C).[1] For complexes derived from anisole, this corresponds to γ-alkylation of an enone (Scheme I). The reactions are also stereospecific providing access to asymmetric synthesis via a metal stabilized cation.[12] Stereochemical course of the reactions can also be controlled taking advantage of the steric bulk of the tricarbonyl iron group.[13]

Some of the nucleophilic reactions involve allylsilanes,[14] O-silylated enolates,[15] enols (derived from ketones and dicarbonyl derivatives)[11] and alkynyl derivatives of boron,[16] zinc,[17] cadmium[17] and copper.[18] Recent applications of these complexes include synthesis of some insect pheromones[19] and terpenes[20] and approach towards tricothecane,[21] aspidospermine,[22] aphidicolin[4b] and steroidal[23] ring systems.

This area of organometallic chemistry is still relatively new, and much needs to be understood about the reactivity patterns. It is clear, however, that the use of tricarbonyl(diene)iron complexes provides new pathways for organic transformations and constructions.

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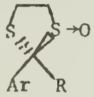
PROPOSED MODEL FOR CHIRAL RECOGNITION OF CYCLIC SULFOXIDES

Reported by Bruce C. Hamper March 8, 1982

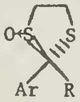
The direct resolution of racemic mixtures by chiral chromatography is desirable both in terms of theoretical implications[1] and practical applications. Enantiomers of a racemate can exhibit different partition coefficients upon a chiral stationary phase (CSP).[2] This results in different retention times for the enantiomers and consequently a direct chromatographic resolution. In 1938, Henderson and Rule were the first to apply these principles successfully[3]; partially resolving p-phenylene-bis-iminocamphor using (+)-lactose as the CSP. Until recently it has been difficult to achieve large enough differences in the partition coefficients for complete resolution.[4] Some notable exceptions include the resolution of chiral helicenes,[5a] chiral arenes[5b] and the resolution of amino acids using either a chiral crown ether as the CSP[6] or by ligand exchange chromatography.[7] Chiral polymers such as polyamides[8a] or poly(triphenylmethylmethacrylate)[8b] have also been successfully employed as stationary phases.

A CSP will exhibit a preferential interaction with one enantiomer only if there is a minimum of three simultaneous, stereochemically dependent interactions between the stationary phase and solute molecule.[1b,9] Based on this premise, we have developed a chiral stationary phase from N-(3,5-dinitrobenzoyl) phenylglycine, CSP-1, which is capable of resolving a variety of functionally different compounds.[10a] CSP-1 contains a π-acidic aromatic group, an acidic and basic site and large steric subunits. Each of the types of compounds resolvable upon CSP-1 contains complimentary subunits: an aromatic moiety to serve as a π-base, a basic site and either an acidic site for hydrogen bonding or a site for steric repulsion.[10b-e]

In order to gain more detailed insight into the requirements for chiral recognition, a number of cyclic sulfoxides, 2,2-disubstituted-1,3-dithiolane-1-oxides **1** and **2**, presumed to meet chiral recognition requirements, were prepared. The two possible diastereomers



1



2

were separated chromatographically and the relative configurations determined by NMR using a lanthanide shift reagent.[11] For a series of sulfoxides we endeavor to relate the elution orders on CSP-I to the absolute configurations of these configurationally unknown compounds. A solvation model with CSP-I can be proposed to enable such a correlation. Independent assignments of absolute configuration have been attempted through NMR studies with a chiral solvating agent[12] and by CD measurements.[13] The degree of agreement between these studies will be discussed as will the validity of the proposed solvation model and the requirements for the design of better CSP's.

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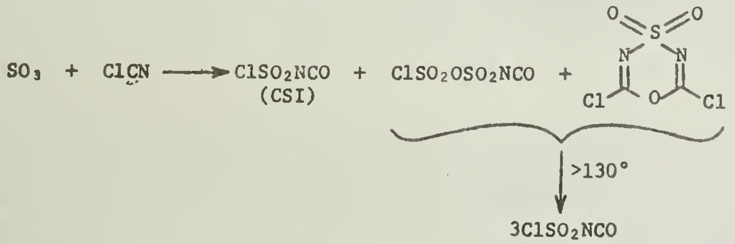
CHLOROSULFONYL ISOCYANATE: A VERSATILE ELECTROPHILIC REAGENT[1]

Reported by Donald H. Champion March 22, 1982

Chlorosulfonyl isocyanate (CSI) is an extremely reactive electrophile which was first prepared by Roderich Graf[2a] in the early 1950's. A variety of nucleophiles react with it forming many products. CSI is useful for preparing heterocycles including β-lactams and uracil derivatives. Because of its reactivity towards olefins, it has been used to study electrophilic additions to olefins[1c-d,3-38] as well as the rearrangement of the intermediate carbocations.[3-17,18b,19-24]

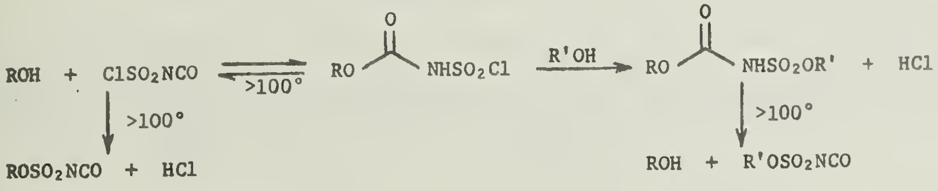
The preparation of CSI[2a-b] involves reaction of cyanogen chloride and sulfur trioxide to produce 2:1, 1:1 and 1:2 adducts. Above 130° the 2:1 and 1:2 adducts revert to CSI (eqn. 1). As expected, CSI is hydrolyzed violently and care must be taken in this regard. It can be stored for reasonable periods in Teflon bottles or glass ampoules. CSI is also commercially available.

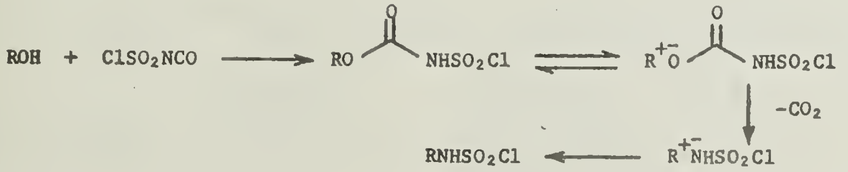


(1)

Reactions with Nucleophiles. Alcohols, thiols, amines, carboxylic acids and amides readily add to the carbon of CSI. The chlorosulfonate group in the products can then be further elaborated or removed by hydrolysis. Carbamates are products from the reaction of alcohols with CSI.[39] In the case of phenols or when the alkoxy group is capable of supporting a negative charge the reaction is reversible above 100°.[40] Alkoxysulfonyl isocyanates are produced by the reaction of an aryl carbamate with an alcohol. The phenol can be removed by heating at 100° or above.[41] At these higher temperatures the products are substituted sulfonyl isocyanates (Scheme I). If R^+ is a stable carbocation the initially formed carbamate ionizes, the anion decarboxylates, and a chlorosulfonamide forms by collapse of the resulting ions (eqn. 2).[42]

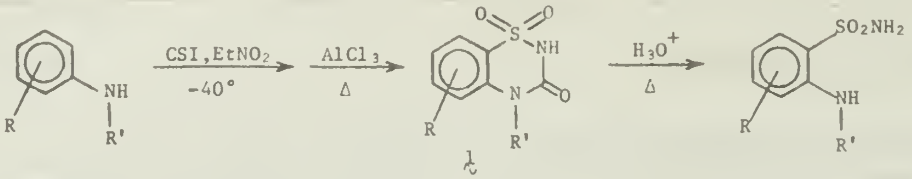
Scheme I



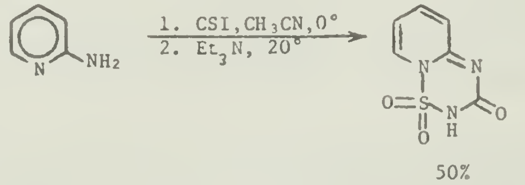


(2)

Amines react with CSI to give ureas. In suitable systems, cyclization affords heterocyclic compounds. Ureas derived from anilines give good yields of 2H-1,2,4-benzothiazidin-3(4H)-one 1,1-dioxides (1) under Friedel-Crafts conditions. Hydrolysis of 1 with hydrochloric or sulfuric acid produces *o*-aminobenzenesulfonamides (eqn. 3).[43] Similarly, 2-aminopyridine or 2-aminopyrazine each give 1,2,4,6-thiatriazene-1,1-dioxide systems (eqn. 4).[44] Treatment of 1H-tetrazol-5-amine with CSI in acetone affords 5-azido-2H-1,2,4,6-thiatriazin-3(4H)-one 1,1-dioxide (2). When 2 is heated in water conversion to (1H-tetrazol-5-yl)urea is accomplished (eqn. 5).[45] If 2-aminobenzophenones are used, cyclization to 4-phenyl-2(1H) quinazolines occurs (eqn. 6).[46]



(3)



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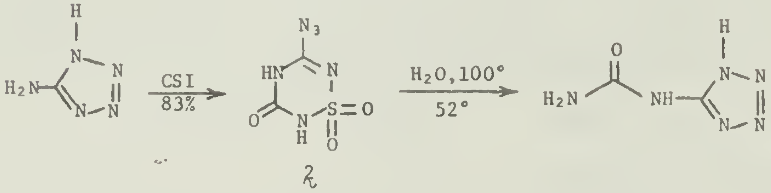

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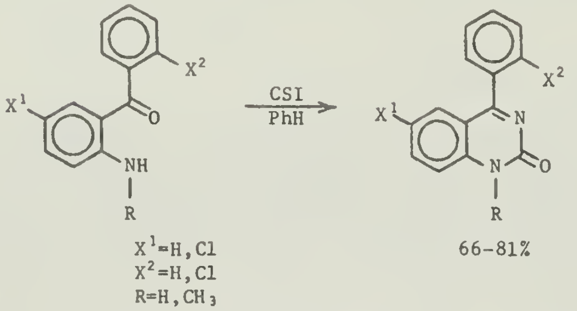
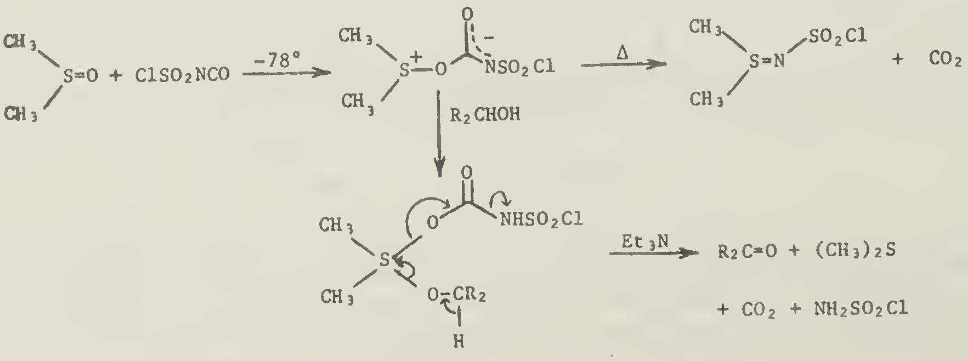


(6)

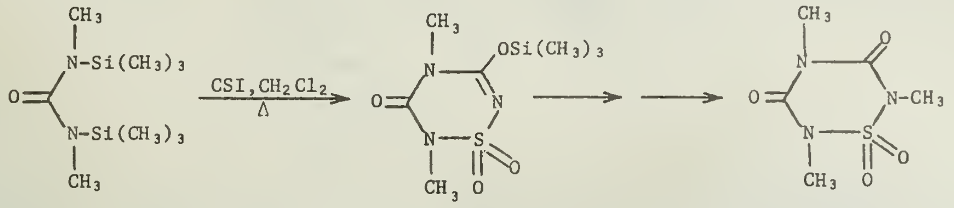
Carboxylic acids can be converted to nitriles in good yield by employing CSI.[47] Nucleophilic attack of the acid on CSI followed by decarboxylation forms N-chlorosulfonyl substituted amides. Heating in dimethylformamide causes loss of sulfur dioxide and hydrogen chloride forming the nitriles. However, similar treatment of formic acid produces formic anhydride.[48] Nitriles may also be obtained by dehydration of aldoximes and amides in the presence of CSI.[49]

Dimethylsulfoxide reacts with CSI at -78° to form a 1:1 adduct which readily oxidizes primary and secondary alcohols.[50] Formation of N-chlorosulfonyldimethylsulfimide occurs by loss of carbon dioxide from the DMSO-CSI adduct above -20° (Scheme II).

Scheme II



CSI reacts with N,N'-dimethyl-N,N'-bis(trimethylsilyl)urea to give the cyclic product 3 quantitatively. Replacement of the trimethylsilyl group with a hydroxyl moiety by treatment with difluorophosphoric acid, followed by formation of the silver salt and alkylation with methyl iodide produces 4 (eqn. 7).[51] Tetramethylisothiourea forms the zwitterionic 1:1 adduct 5 with CSI at low temperature.[52] CSI reacts with 2-aminothiazoline in cold acetonitrile and, following addition of ethyldiisopropylamine, the cyclic product 6 is obtained.[53]

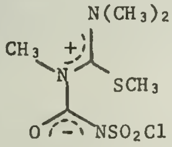


3 4

(7)

Reaction with Aldehydes, Ketones and Imines. At temperatures in excess of 0° aldehydes are transformed into azomethine-N-sulfonyl chlorides.[1c] With ketones reaction is not as simple. Many types of products are formed depending on the structure of the ketone and reaction conditions.

Enolizable ketones produce N-chlorosulfony-β-ketocarboxamides[54-55] upon reaction with CSI which in turn produce β-ketonitriles upon treatment with DMF.[56] A second molecule of CSI may add to the ketocarboxamides to give malonamide derivatives (eqn. 8).[54] Aryl ketones with an α-methylene link cyclize to 1,2,3-oxathiazin-4-(3H)-one 2,2-dioxides (eqn. 9).[54-55] The enol of a β-carboxamide can also cyclize after adding another mole of CSI to provide 2H-1,3-oxazine-2,4(3H)-diones (7) in low to moderate yields.[54-55] Uracils can be obtained quantitatively from 7 by reaction of ammonia (eqn. 10).



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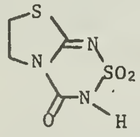

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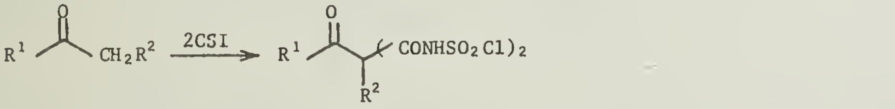

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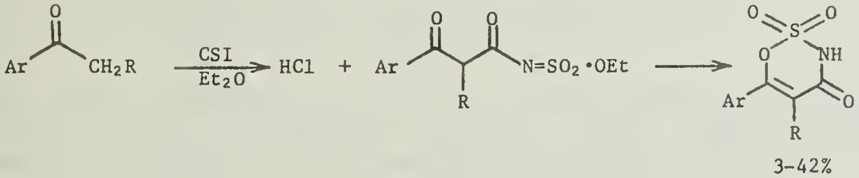

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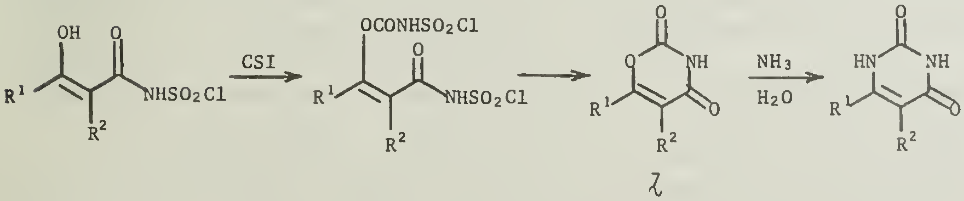
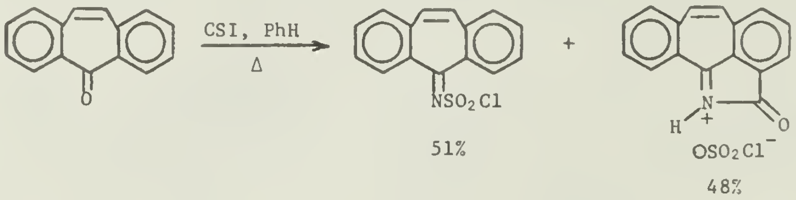


7
3-71%

(10)

Non-enolizable ketones react at the carbonyl and loss carbon dioxide yields imines. 4-Pyrones react in this manner.[57] 2-Phenyl-5-oxo-5-H-naphtho[1,8,bc] thiophene affords the corresponding N-chlorosulfonylimine in 94%.[58] In the case of 5H-dibenzo[a,d]cyclohepten-5-one, the imine and a cyclic product are obtained (eqn. 11).[59] Cyclic products are also obtained when α,β-unsaturated ketones react with CSI (eqn. 12).[53,60]



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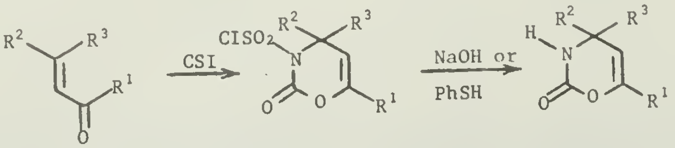
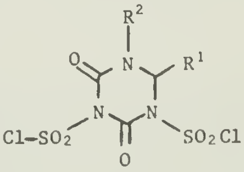


(12)

Imines and aryl azines cyclize with two moles of CSI giving products 8 and 9.[61]



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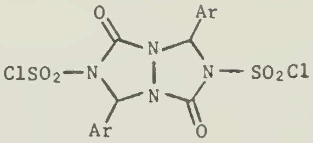
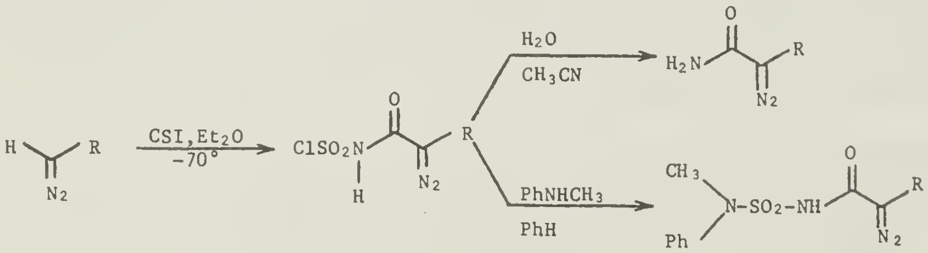


9

Acylation by CSI. Aromatics may be acylated in good yield using CSI.[47,62-63] The tribenzylether of 1,3,5-trihydroxybenzene is acylated and following hydrolysis the benzoic acid amide is formed.[62] Reaction of indoles gives indole-3-carboxamides, acids and nitriles in yields of 60-80%.[63] Carboxamides and nitriles of other aromatics are produced in a similar fashion.[47]

Diazo compounds are also acylated when treated with CSI. The chlorosulfonyl group can be removed hydrolytically or reacted with N-methylaniline to give N-(N-methylaminosulfonyl)-α-diazocarboxylic acid amides (eqn. 13).[64]

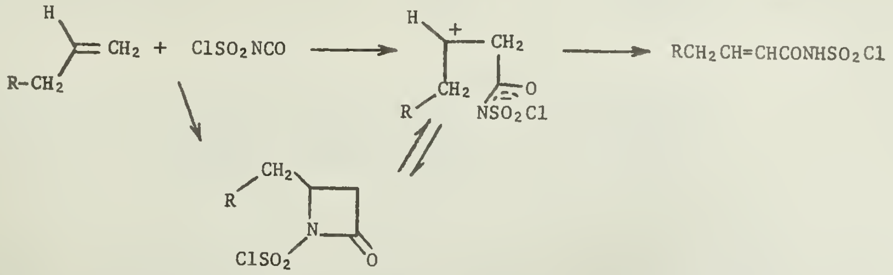


(13)

Reaction with Olefins. The most studied reactions of CSI have been those involving carbon-carbon multiple bonds, particularly olefins. Products from these reactions vary, but barring radical reactions, the first step is considered to be formation of a β-lactam or zwitterionic intermediate. The identity of the initially formed intermediate is a question of considerable debate.

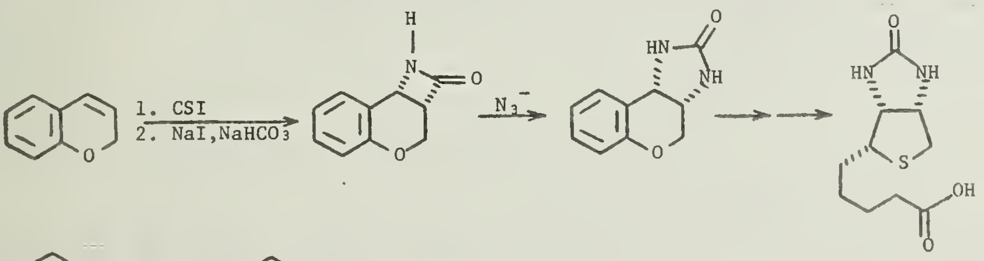
CSI reacts with a variety of olefins to give β-lactams or unsaturated amides. Higher temperatures slightly favor formation of the amides. Both products can be thought of arising from an intermediate zwitterion which undergoes ring closure or proton transfer (Scheme III). As expected, the formation of the carbon-nitrogen bond occurs at the carbon most able to support positive charge. Thus reactions are regiospecific and reactivity parallels the stability of the carbonium ion. However, they are also stereospecific[1d,25] which suggests a concerted pathway to the β-lactams. But because of the variety of products, rearrangement of carbonium ion intermediates and the fact that the reaction proceeds faster in more polar solvents,[1d] a stepwise mechanism is generally accepted.

Scheme III

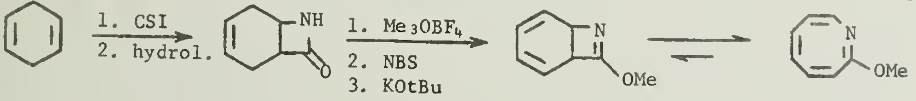


The N-chlorosulfonyl-β-lactams are often rather reactive due to the chlorosulfonyl functionality. Parent lactams can be isolated by reductive hydrolysis of the chlorosulfonyl group with benzenethiol and pyridine or sodium sulfite.[1c] N-Chlorosulfonyl-β-lactams may also be converted to unsaturated nitriles in 20-75% by heating in DMF.[65] In this connection, unsaturated nitriles which result in addition of CSI with the opposite regiochemistry can be formed by using a trimethylsilyl derivative.[26]

CSI is useful for the synthesis of the benzyl ester of antibiotic PS-5,[66] carbopenams,[67] and β-lactam prostaglandins.[68] Using the unlikely looking starting material chromene, (±)-biotin may be synthesized.[69] Initial formation of the β-lactam leads to the cis stereochemistry of the urea part. Attack of azide ion on the lactam followed by Curtius degradation gives the cyclic urea in 56% overall yield. Further reactions afford biotin (eqn. 14). 2-Alkoxyazocines can be formed by treatment of 1,4-cyclohexadienes with CSI followed by reductive hydrolysis leading to the β-lactams.[70] Allylic bromination of the 2-methoxyazetines, dehydrobromination and electrocyclic ring expansion of the 7-azabicyclo[4.2.0]octatriene systems produces the azocines (eqn. 15).



(14)

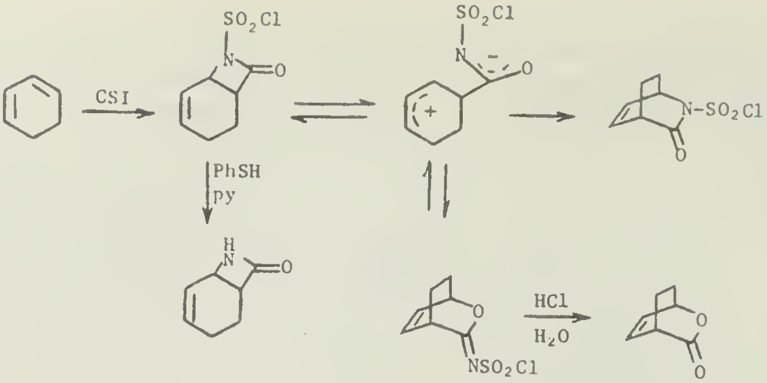


(15)

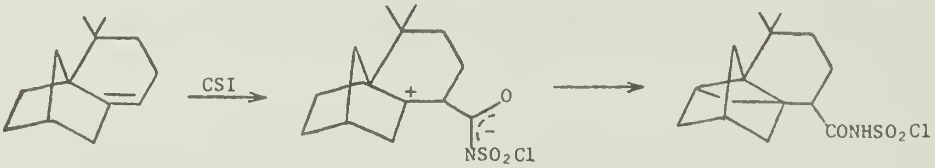
When more complicated olefins are employed rearrangements of the intermediate zwitterion are common. Conjugated dienes form products from 1,4-cyclizations in addition to β-lactams.[24,38] One study by Malpass and Tweddle[3] shows cyclopenta-, cyclohexa- and cyclohepta-1,3-dienes give 1,2- and 1,4-cycloadducts depending on the diene and reaction conditions. β-Lactams form initially and rearrange (Scheme IV). Smaller ring systems rearrange with greater facility. Cycloheptatriene[4] and the iron tricarbonyl complex of cyclooctatetraene[27] behave similarly.

CSI is useful for studying modes of addition and rearrangements in olefinic systems.[5-17 28,29] Some more recent examples are the polycyclic sesquiterpenes[31] longifolone, isolongifolene, α-cedrene, caryophyllene and thujopsene, vinylcyclopropanes,[18] 7-substituted norbornadienes,[19] barrelenes,[20] and 11-methyleneoanthracene.[21] Among the sesquiterpenes only isolongifolene gives a rearrangement

Scheme IV



product (eqn. 16). The others yield β-lactams or an unsaturated amide in the case of α-cedrene. Cyclic compounds **10a-c** undergo cycloadditions with CSI to give β-lactams. Interestingly, **10a** and **b** do not react with tetracyanoethylene.[18a] In the case of **10c**[18b] the β-lactam product is thermally labile and rearranges. Different rearrangement products are isolated depending on the conformation of the isopropylene group in the zwitterionic intermediate. The 7-substituted norbornadienes produce a β-lactam and an iminolactone.[19] This constitutes the first case of endo addition of CSI to a norbornadiene. Barrelene reacts similarly but it also gives the 5-membered lactam. Benzofused barrelenes rearrange to bicyclo[3.2.1]octa-1,5-diene skeletons.[20] The same skeleton is formed on treatment of 11 with CSI.[21] In addition to olefins, CSI may be used in reactions with strained saturated hydrocarbons.[32-33]



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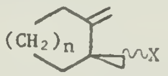
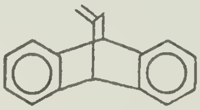


10 a, X=CN
b, X=CO_2CH_3
c, X= $\underset{CH_3}{C}{=}CH_2$
n=2,3

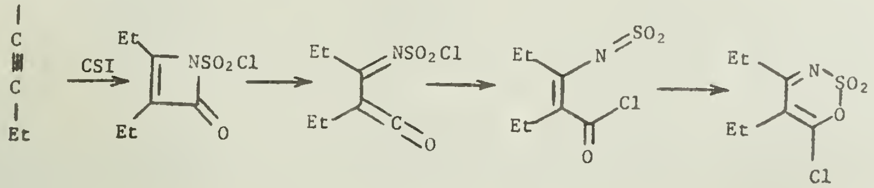


11

Under conditions for radical formation olefins may insert in the sulfur-chlorine bond of CSI or produce 2:1 cyclic adducts. At 65-75°C the insertion products are formed and at lower temperatures (20°) with excess olefin the cyclic products are formed. Yields range from 3-92% for the insertion products and 60-80% for the cyclic products. Chlorinated olefins give lower yields and in the case of 4,6,6-trichloro-1-hexene the yield is only 3%.[71]

Reaction with Allenes. Reactions with allenes normally proceeds with electrophilic addition at the central carbon to give an allylic carbonium ion intermediate. Products are methylene-β-lactams and unsaturated amides.[25] With alkenylidenecyclopropanes attack occurs at the carbon remote to the cyclopropyl ring.[72-74] β-Lactams thus formed can be hydrolysed with water followed by barium hydroxide to form ketones.[73] If the cyclopropyl ring is phenyl substituted addition to the central carbon is followed by cyclopropyl ring opening.[75-76] 2-Phenylisobutenylidenecyclopropane reacts with CSI forming a mixture of products which varies with temperature.[74] This reaction is stereospecific at low temperatures but at higher temperatures it is not. Asymmetric substitution on the terminal carbon remote to the cyclopropyl ring shows that stereoselectivity is not as great with respect to the E-Z relationship of the exocyclic methylene.[76]

Reaction with Acetylenes. Acetylenes react with one mole of CSI producing heterocyclics as in the case of 3-hexyne. The proposed mechanism (eqn. 17) involves formation of the unsaturated β-lactam followed by ring opening, chlorine migration and ring closure through oxygen. An x-ray structure determination offers conclusive evidence for **16**.[77] Other acetylenes show similar reactivity.[78]



(17)

16

In conclusion, CSI is an attractive synthetic reagent for the preparation of a diverse array of compounds. Its possession of two reactive centers lends to the formation of heterocycles. Perhaps the most useful transformations of CSI involve heterocycles as products. It is also important for elucidating transformations of polycyclic olefins.

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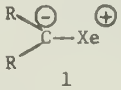
SYNTHESIS AND CHEMISTRY OF DIAZOTETRAKIS(TRIFLUOROMETHYL)CYCLOPENTADIENE

Reported by Eugene P. Janulis March 25, 1982

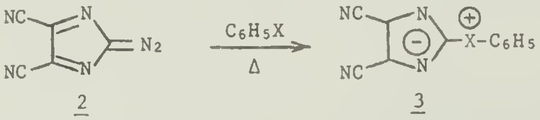
Since Bartlett's pioneering work in xenon chemistry,[1] the synthesis of a compound in which xenon is bonded to carbon has been a target of interest. Ion cyclotron resonance studies have suggested that the strength of the xenon-carbon bond for CH_3Xe^+ to be in the range of 43 ± 8 kcal mol^{-1}.[2] This fact and DesMarteau's recent synthesis of $FXeN(SO_2F)_2$,[3] suggests that the synthesis of an organo-xenon compound is possible. All of the known compounds of xenon have highly electronegative substituents. It is resonable then to expect that the synthesis of an organo-xenon compound will involve a highly electronegative carbon site.

One method that appears feasible involves the reaction of a carbene with xenon to give a zwitterionic compound of the type 1.

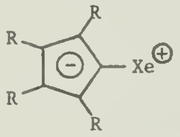


1

The reactive intermediate formed by the loss of nitrogen from diazodicyanoimidazole (2) inserts a 4,5-dicyanoimidazole moiety into various substrates.[4] This intermediate is unusually electrophilic and attacks the halogen of aryl halides to form novel halonium ylides (3) among other



products. The possibility of synthesizing an organo-xenon compound with the general structure 4, a "xenone", has been investigated. R should be a



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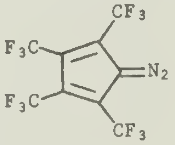

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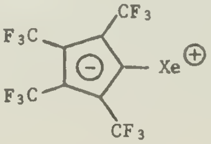
strong electron attracting group. It was hoped that this type of structure would stabilize the zwitterionic nature of 1 and thus increase the strength of the carbon-xenon bond.

In the course of this investigation diazotetrakis(trifluoromethyl) cyclopentadiene (5) has been synthesized.[5] The chemistry of the highly reactive intermediate obtained from the loss of nitrogen from 5, along with a number of ylide formation reactions, will be discussed. Preliminary evidence for the synthesis of the xenone (6) will also be presented.



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NEW SYNTHETIC METHODS FOR α-METHYLENE-γ-BUTYROLACTONES AND THEIR DERIVATIVES

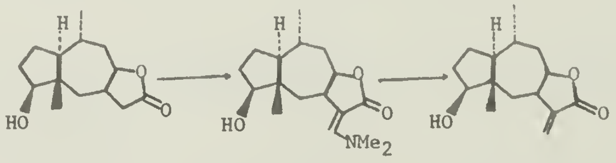
Reported by Myung Ho Hyun March 29, 1982

The α-methylene-γ-butyrolactone ring is present as a structural unit in a wide variety of sesquiterpenes and other naturally occuring compounds.[1] Many of these compounds show considerable antitumor,[2] root growth inhibitory,[3] antibacterial and allergenic activities.[4] It has been suggested that the biological activities of these compounds arise from their ability to act as alkylating agents by virtue of the conjugate addition of biological nucleophiles such as L-cysteine or sulfhydryl-containing enzymes to the α-methylene lactone moiety.[5] Some of the recently isolated natural compounds containing α-alkylidene-β-hydroxy-γ-butyrolactone units also show similar biological activities.[6] Therefore, the development of synthetic methods for these α-methylene-γ-butyrolactone units has aroused considerable attention in order to approach the total synthesis of the more active members of this group.

Since the appearance of several reviews on the synthesis of α-methylene-γ-butyrolactones,[7] new synthetic methods have been developed and applied to the synthesis of these compounds. In this abstract, synthetic methods developed in the last three to four years will be reviewed briefly.

Introduction of α-methylene groups onto preformed lactone rings: The widely-employed and well-known methods are the introduction of α-methylene groups onto preformed lactone rings via the enolates of the latter.[7] This approach was used in the recent total synthesis of vernolepin,[8] frullanolide[9] and eriolanin.[10] These methods necessarily use strong bases such as LDA to generate the enolates. Therefore, these methods sometimes are not easily reconciled with highly functionalized natures of many of the natural-product target molecules.

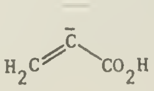
In 1981, Ziegler accomplished the incorporation of the methylene group onto a preformed lactone ring in the total synthesis of (±)-aromatin by a new procedure that did not use strong bases.[11](eq.1) Intermediate lactone 1 was treated with Bredereck's reagent,[12] affording vinylogous carbamate 2 in nearly quantitative yield. The vinylogous carbamate 2 was reduced by treatment with DIBAL to provide α-methylene lactone 3 upon workup.



(1)

1 2 3

Incorporation of acrylate units: Another general approach to α-methylene-γ-butyrolactones is the direct introduction of intact acrylate units through the α-anion 4, of acrylic acid derivatives, the synthetic equivalents of this acrylic acid anion, or the use of intermediates that are equivalent to the allylic anoin derivative 5, of methacrylic acid.



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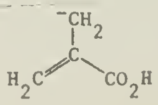

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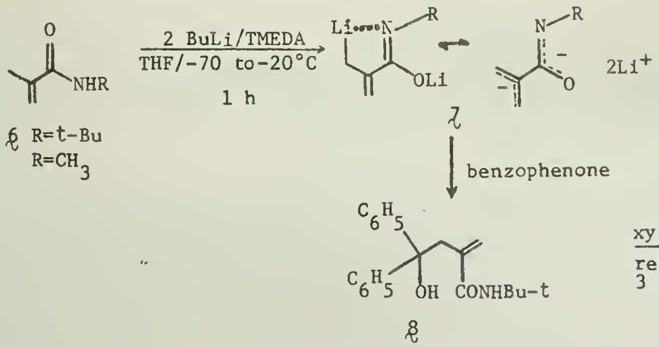
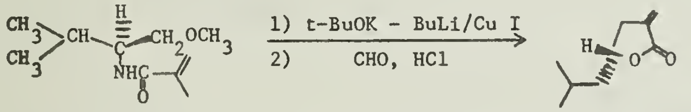
In 1980, the synthetic equivalents of 5, dianions of N-substituted methacrylicamide or more highly substituted cyclic and acyclic acrylamides, were successfully generated and applied by three different research groups to the synthesis of α-methylene or alkylidene-γ- butyrolactones and α-substituted acrylamides.[13]

One example of the synthesis of α-methylene-γ-butyrolactone is shown in Scheme 1. The dianion 7 was produced by treatment of a solution of amide 6 and TMEDA with two equivalents of n-butyllithium. This dianion can react with ketones, aldehydes, halides, and epoxides. Reaction with benzophenone followed by aqueous workup gives the amide 8. The prolonged heating of 8 gives α-methylene-γ-butyrolactone 9.

Scheme 1

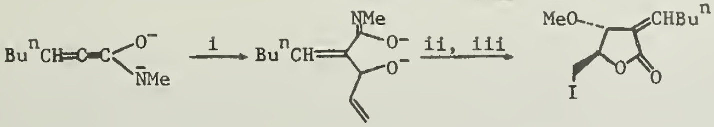


The dianion of N-(o-methoxyphenyl)-2-methylpropenamide was generated on treatment of the amide with potassium tertiary butoxide-butyllithium complex.[13c] The final lactonization was accomplished by hydrolysis in 10% hydrochloric acid. This method was applied to the asymmetric synthesis of α-methylene-γ-butyrolactone using the chiral amide prepared from L-valine (eq.2).

 (2)

In 1981, Barret, et.al.[14] reported the preparation of the allenic dianions, 1-lithio-oxy-1-lithio-amino-allene derivatives. These dianions were used as synthetic equivalents of lithio-acrylates in the synthesis of a substituted β-hydroxy-α-alkylidene-γ-butyrolactone (Scheme 2).

Scheme 2

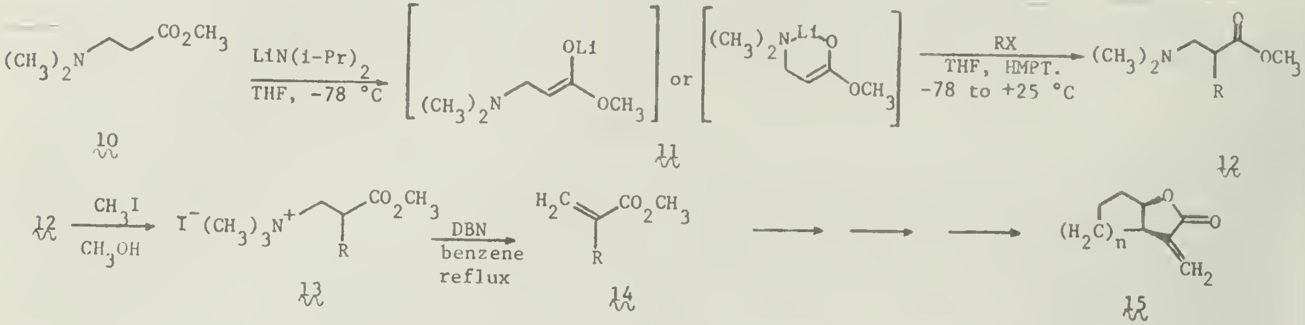


Reactions i and ii were carried out in 1,2-dimethoxyethane, and iii in tetrahydrofuran. i CH_2=CHCHO,-78°C; ii MeI, 25°C; iii I_2, H_2O, 25°C

In recent years, several synthetic equivalents of acrylate α-anion in which the double bond can be introduced later were used in the synthesis of α-methylene-γ-butyrolactones as an alternative to the methods just mentioned. Here, the acrylate unit is introduced in a conveniently protected form, an important consideration in the multistep synthesis of complex natural products in view of the high reactivity of α,β-unsaturated acid derivatives.

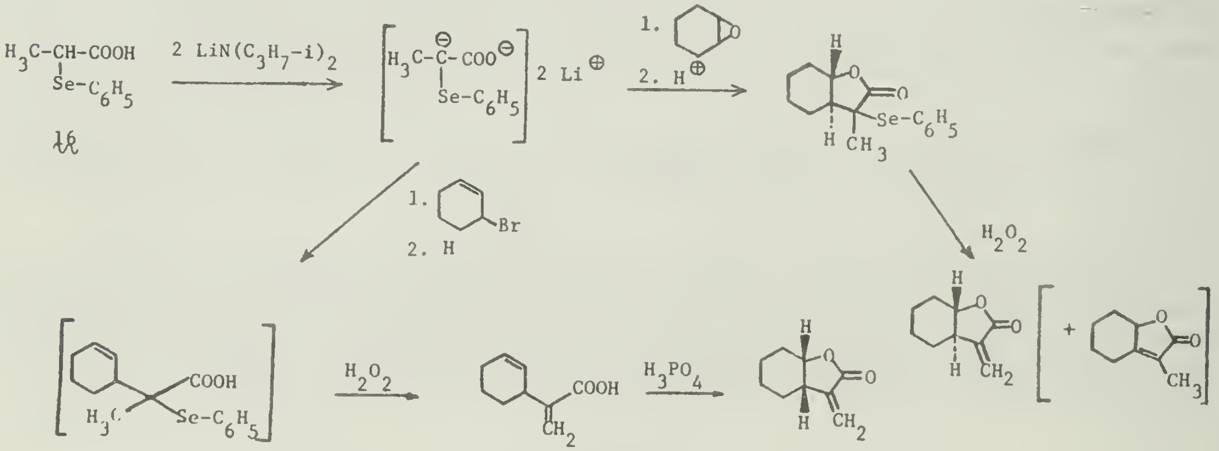
Methyl 3-(dimethylamino) propionate (10) was used as an acrylate synthon in the synthesis of several α-methylene lactones.[15] (Scheme 3) The enolate of 10, generated by LDA, reacts with alkyl halides to produce the corresponding 2-substituted propionates 12. Quaternization of 12 with methyl iodide followed by DBN-promoted elimination gives the 2-substituted acrylates (14). When the alkylating agents are allylic halides, the 2-substituted acrylates give the α-methylene lactone 15, iodolactonization being one of several necessary steps.

Scheme 3



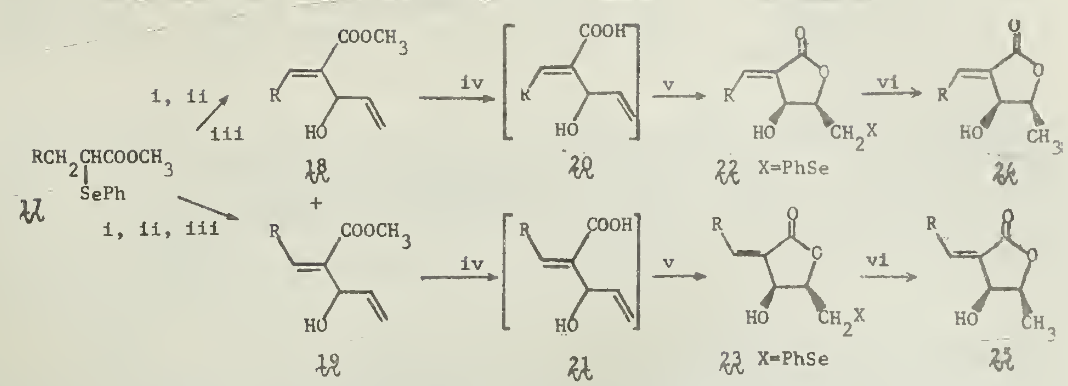
2-Phenylselenopropanoic acid can be a useful synthon for the stereoselective synthesis of both trans- and cis-fused α-methylene lactones.[16] (Scheme 4) The trans isomer was obtained through the direct construction of the lactone ring from the cyclohexene oxide and the dilithio derivative of 16, followed by oxidation and selenoxide elimination. The cis isomer was obtained either by iodolactonization or acid-promoted lactonization.

Scheme 4



Katzenellenbogen and co-workers[17] have recently reported a general method for the synthesis of α-alkylidene-β-hydroxy-γ-butyrolactones using substituted α-phenylselenyl esters as acrylate α-anion synthons. The α-phenylselenyl esters can be oxidized to the selenoxide and subsequently undergo syn elimination under mild conditions. It is said that β-hydroxy selenoxides eliminate to allylic alcohols in preference to enols.[18] Therefore, the α-phenylselenyl esters can be useful synthons in the synthesis of α-alkylidene-β-hydroxy-γ-methylbutyrolactones. Scheme 5 shows the synthesis of α-alkylidene-β-hydroxy-γ-methylbutyrolactones. The enolate anion of α-phenylselenyl ester 17 was quenched with acrolein, followed by oxidation and selenoxide elimination to afford olefinic esters 18 and 19. After the hydrolysis of the olefinic esters to the corresponding carboxylic acids (20, 21) with Claisen's alkali at room temperature, the lactonization of these acids was accomplished by either phenylselenolactonization or iodolactonization. Finally lactones 24 and 25 were obtained by treatment with tri-n-butyltin hydride.

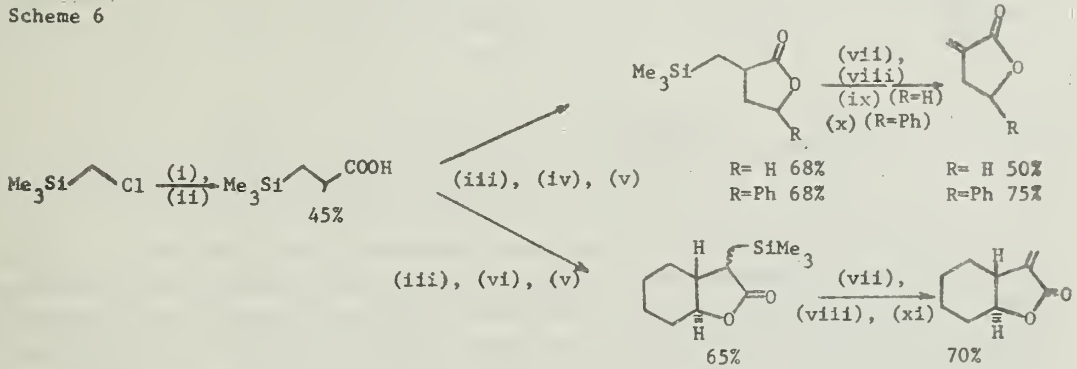
Scheme 5



$R=CH_3(CH_2)_{12}$; $R=CH_3(CH_2)_{14}$. (i) LDA,THF,-78°C; (ii) $CH_2{=}CHCHO$,-78°C; (iii) H_2O_2, H_2O, 0 → 25°C; (iv) KOH, H_2O, CH_3OH; (v) PhSeCl, CH_2Cl_2, 25 °C; (vi) n-Bu_3SnH, PhH, Δ.

β-Trimethylsilylcarbonyl compounds can be brominated and desilylbrominated to place a double bond between the carbonyl group and the β-carbon atom to which the silicon had originally been bonded. Therefore, it is possible to use β-silylcarbonyl compounds as acrylate synthons in the synthesis of some α-methylene-γ-butyrolactones (Scheme 6).[19]

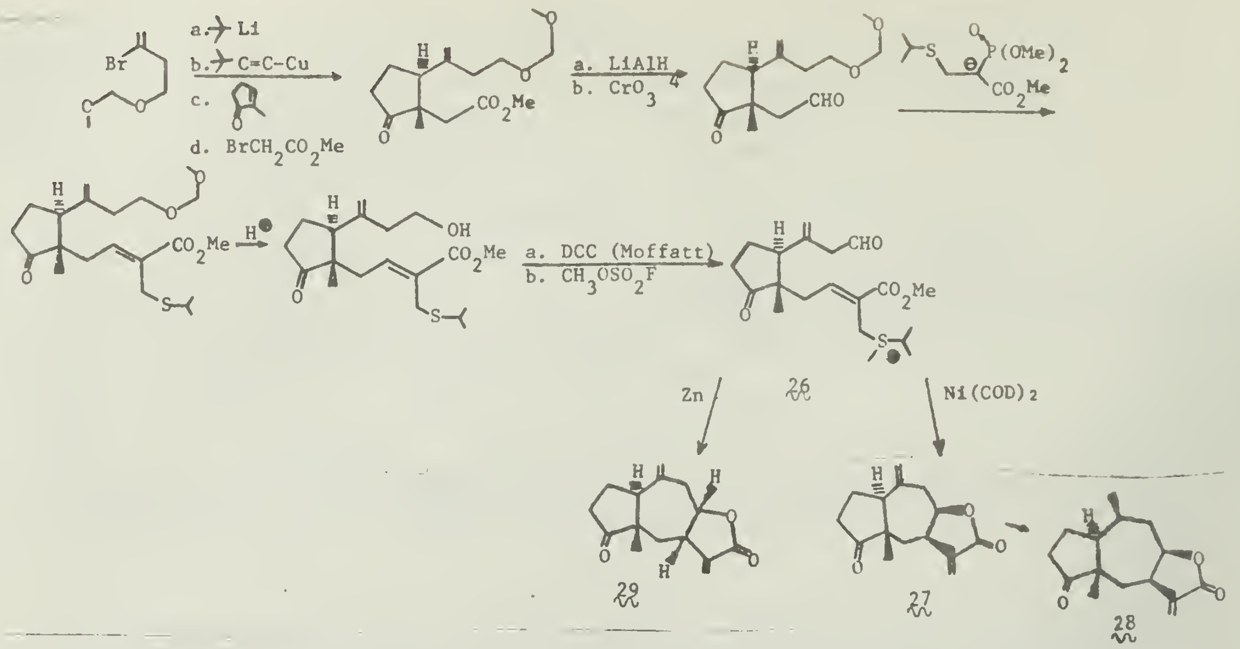
Scheme 6



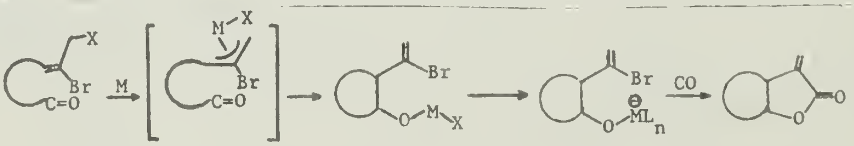
(i) LDA-MeCN; (ii) $KOH\text{-}H_2O_2\text{-}H_2O$; (iii) 2LDA-THF, 0°C; (iv) $R\text{-}\overset{O}{CH_2\text{-}CH_2}$, 20°C; (v) TsOH toluene, reflux; (vi) cyclohexene oxide-THF, reflux; (vii) LDA-THF, -78°C; (viii) $Br_2\text{-}CCl_4$, -78°C; (ix) $Al_2O_3\text{-}CH_2Cl_2$-reflux; (x) CsF-DMF, 20°C; (xi) $PhCH_2NMe_3F$-THF, 20°C.

Metal-promoted cyclization/lactonization and cyclization/carbonylation: The formation of α-methylene lactones through the reaction of allyl organometallics with ketones is mentioned in other reviews.[7] These reactions give only acyclic and spiro methylene lactones. However, an intramolecular version of this reaction has been successfully employed in the total synthesis of confertin (28) by Semmelhack (Scheme 7).[20] The synthetic strategy of this reaction involves the cyclization by intramolecular coupling of an allylic metal species with an aldehyde unit followed by spontaneous lactonization. Ring closure of 26, promoted with excess bis(1,5-cyclooctadiene) nickel gives the cis-fused-α-methylene lactone 27. On the other hand, ring closure with zinc/copper couple give compound 29 having the unnatural α-configuration.

Scheme 7



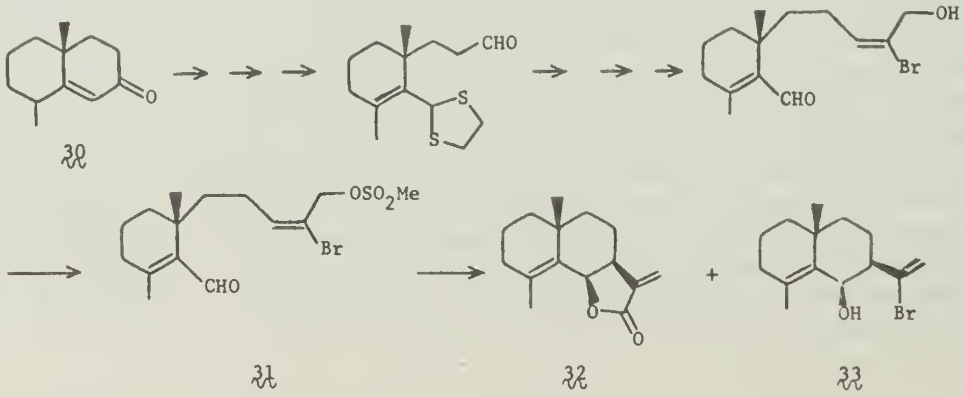
The formation of α-methylene lactones using nickel carbonyl to promote intramolecular alkoxy carbonylation of vinyl halides have been reported recently.[21] This intramolecular carbonylation involves zero valent nickel, as does a related reductive cyclization method mentioned earlier. Therefore, the carbonylation procedure can be combined into a simple method for α-methylene lactone synthesis, where nickel carbonyl leads to two different carbon-carbon coupling steps.[22] The general procedure is summarized in eq.3.



(3)

By this nickel-promoted cyclization/carbonylation procedure, (±)-frullanolide (32) has been synthesized stereospecifically (Scheme 8). The E isomer of methansulfonate ester 31, prepared from dimethyloctalone 30 through a series of several conventional steps, was cyclized and carbonylated with nickel carbonyl affording frullanolide and intermediate 33 with complete conversion. The latter product was converted to frullanolide upon treatment with excess nickel carbonyl and triethylamine in benzene. The same reaction with the Z isomer also gave frullanolide (10%) and intermediate 33 (40%). The formation of the same ring fusion isomer from both the E and Z isomers

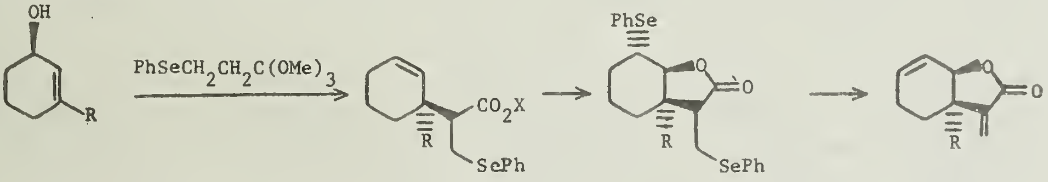
Scheme 8



may result from the rapid isomerization of the allylic double bond during formation of the common allyl-nickel intermediate. The reason for the very high selectivity for the cis ring fusion and the syn orientation of the lactone ring with respect to the angular methyl group is not yet clear.

Rearrangement: In several syntheses of α-methylene-γ-butyrolactone derivatives, the acrylate units were introduced through rearrangement reactions. Since Still's total synthesis of (±)-frullanolide via a modified Claisien rearrangement,[23] acrylate units have been introduced through rearrangement reactions in several syntheses of α-methylene-γ-butyrolactones and their derivatives.

A Claisen ortho ester rearrangement was successfully employed by Raucher *et al*. in the synthesis of several α-methylene-γ-butyrolactones (eq. 4).[24] Compound 35 was obtained through the Claisen ortho ester rearrangement of 2-cyclohexen-1-ol (34) with trimethyl 3-(phenylseleno)ortho propionate. The cis-fused α-methylene-γ-butyrolactone 36 is available by a selenolactonization of 35 and oxidative elimination of both phenyl seleno groups.

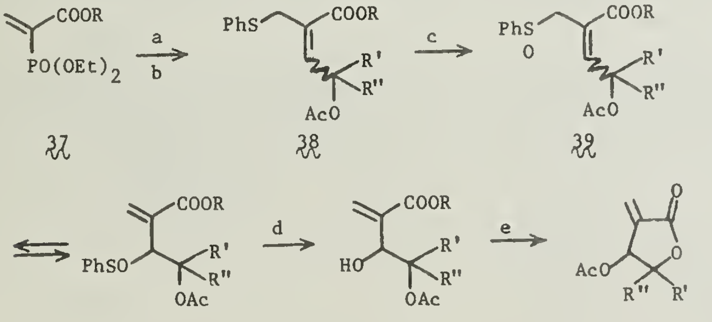


(4)

34 35 36

Benezra has recently described the synthesis of β-acetoxy-α-methylene-γ-butyrolactone[25] through the allylic sulfoxide rearrangement. β-Hydroxy-α-methylene-γ-butyrolactone is essentially the allylic alcohol derivative. So, it seemed natural to use the allylic sulfoxide rearrangement to get allylic alcohol derivatives. Scheme 9 summarizes this reaction. Michael addition of phenylsulfide to phosphonate 37 and treatment with α-acetoxy aldehyde gives allylic sulfide 38. This allylic sulfide was oxidized to give sulfoxide 39. Sulfoxide 39 and sulfenate 40 equilibrate at room temperature. This equilibrium was shifted by adding one equivalent of trimethyl phosphite in methanol, giving allylic alcohol 41. Allylic alcohol 41 was finally cyclized to β-acetoxy-α-methylene-γ-butyrolactone.

Scheme 9



37 38 39

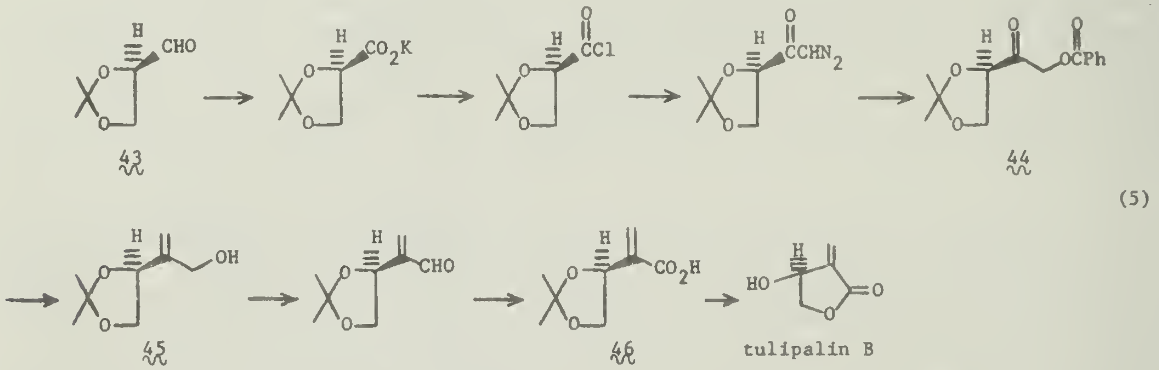
40 41 42

(a) PhSNa, (b) R'R"C(OAc)CHO, (c) m-CPBA, (d) $P(OMe)_3$, (e) p-TsOH.

The allylic alcohol moiety in β-hydroxy-α-alkylidene-γ-butyrolactone was also introduced through the allylic selenoxide rearragnement in the total synthesis of (±)-litsenolide C_1 by Wollenberg.[26]

Miscellaneous: The cycloaddtition reaction of ketenes to olefins,[27] the Eschenmoser type cycloaddititon reaction[28] and the ene reaction[29] were successfully employed in the synthesis of α-methylene-γ-butyrolactones and their derivatives.

Recently, optically active tulipalin B was synthesized starting from isopropylidene-D-glyceraldehyde by Tanaka and Yamashita.[30] (eq. 5) Isopropylidene-D-glyceraldehyde 43 was converted to keto benzoate 44 through alkaline permanganate oxidation, oxalyl chloride, diazomethane treatment and, finally, heating with benzoic acid in the presence of copper powder. The α-methylene group in the final product was introduced at this stage by Wittig reaction of 44 with methyltriphenylphosphonium iodide and n-butyllithium. Olefinic alcohol 45 obtained from the Wittig reaction of 44 was converted to the pure olefinic carboxylic acid 46 in good yield through two consecutive oxidations with manganese dioxide and silver oxide. Finally, optically pure tulipalin B was obtained by acid hydrolysis of 46.



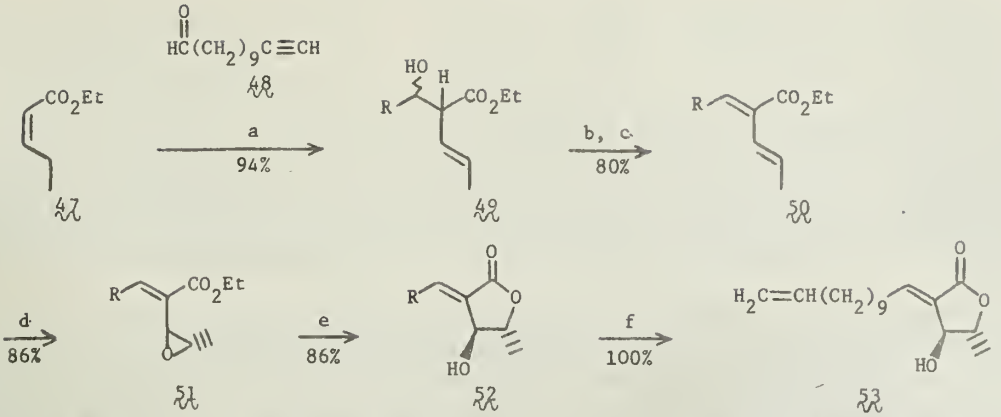
43 44 (5)

45 46 tulipalin B

In 1982, Kende reported a stereospecific route to the α-alkylidene-β-hydroxy-γ-butyrolactone system.[31] The basis for this route is that deconjugative protonations, alkylations and aldol condensations of the dienolates from (Z)-2-alkenoates give the corresponding (E)-3-enoate products, whereas dienolates from (E)-2-enoates give mainly the (Z)-3-enoate products.[31,32]

The stereospecific deconjugative aldol condensation has been exploited in the total synthesis of litsenolides 52 and 53. (Scheme 10) Ethyl (Z)-2-pentenoate 47 was treated with LDA at -78°C to give dienolate. Addition of 11-dodecynal 48 to this dienolate followed by neutral workup gave 1:1 mixture of the diastereomeric pair of 3-E-isomers 49 in 94% yield. This mixture was mesylated and then MsOH was eliminated by treatment of the mesylates with KH to give exclusively the single diene ester 50. Chemoselective epoxidation of the diene ester 50 was accomplished using MCPBA to yield epoxide 51. Acid-catalized cyclization of epoxy ester 51 gave (±)-litsenolide B_2 52. Hydrogenation of 51 using Lindlar catalyst quantatively gave (±)-litsenolide A_2 53.

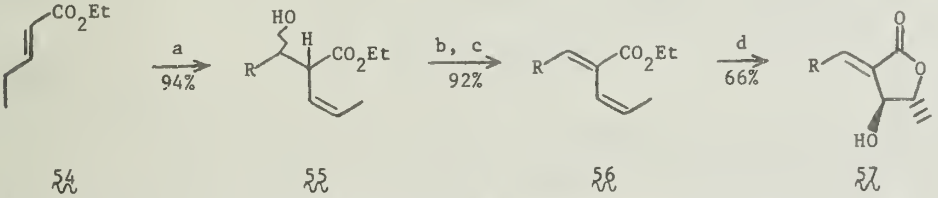
Scheme 10



R = $HC{\equiv}C(CH_2)_9$; a = LDA, HMPA, THF, 4 h, -78 °C, 20 min; b = 1.05 equiv of MsCl, 1.5 equiv of Et_3N, CH_2Cl_2, 0 °C, 15 min; c = 2 equiv of KH, THF, 0 °C → room temperature, 12 h; d = 1 equiv of m-CPBA, 1 equiv of K_2CO_3, CH_2Cl_2, 0 °C, 2 h; e = 2 N H_2SO_4 (cat.), THF, Δ, 8 h; f = H_2, 1 atm, 5% Lindlar catalyst, EtOAc, 1 h.

The stereochemical course of these reactions was confirmed by an independent sequence leading to litsenolide C_2 from ethyl (E)-2-pentenoate. (Scheme 11) Aldol condensation of the enolate from 54 with tetradecanal gave the diastereomeric pair of Z isomers 55 in 94% yield. Mesylation and elimination of MsOH gave a single diene ester 56. Osmylation at the disubstituted double bond and then lactonization by 2N HCl gave (±)-litsenolide C_2 57 in 66% yield. When the epoxidation-lactonization sequence was applied to diene ester 56, (±)-epilitsenlide C_2 was obtained in 80% yield.

Scheme 11



R = $CH_3(CH_2)_{12}$; a = LDA, HMPA, THF, -78 °C, n-$C_{13}H_{27}CHO$, 20 min; b = 1.05 equiv of MsCl, 1.5 equiv of Et_3N, CH_2Cl_2, 0 °C, 15 min; c = 1 equiv of KH, THF, 0 °C → room temperature, 12 h; d = 0.2 equiv of OsO_4, 1.05 equiv of NMO, 2 equiv of t-BuOH, aqueous acetone, room temperature, 24 h, then 10% aqueous HCl, room temperature, 4 h.

Conclusion: Several possible synthetic pathways to the synthesis of α-methylene-γ-butyrolactones and their derivatives have been described briefly. These methods possibly can be used for the total synthesis of the biologically more active compounds.

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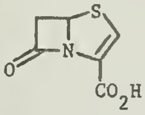
PENEM β-LACTAM ANTIBIOTICS: A STRUCTURAL AND SYNTHETIC PERSPECTIVE

Reported by Michael J. Sofia April 1, 1982

Since Alexander Fleming's discovery of penicillin in 1929, β-lactam antibiotics have become very important agents in combatting human bacterial infection. The penicillins, originally isolated from Penicillium notatum, were the first generation β-lactams, and the cephalosporins first isolated from cephalosporium aeremonium were the second generation β-lactams.[1]

With the need for antibiotics having a broader activity spectrum and more effectiveness against Gram-negative bacteria and anaerobic bacteria as well as resistance to β-lactamase enzyme, new generations of β-lactams are being developed.[1] A new class of β-lactam antibiotics, the non-classical bicyclic β-lactams, represented by penemcarboxylic acid, clavulanic acid, and N-formimidoylthienamycin, no longer contain the familiar cephem or penam nucleus but have a modified β-lactam fused ring system.

The penemcarboxylic acid, originally developed by Robert B. Woodward and coworkers,[2] is representative of the logical approach in antibiotic development.



penemcarboxylic acid

Mode of Action. When a penicillin-sensitive cell grows in the presence of penicillin, the integrity of the cell wall is lost and the cell wall either ruptures or its membrance is damaged beyond repair. This phenomenon of cell wall destruction was studied extensively by Strominger and coworkers.[3]

Bacterial cell walls are composed of polysaccharide chains consisting of two alternating sugars, N-acetylglucosamine and 3-O-D-lactic acid ether of N-acetylglucosamine which is called N-acetylmuramic acid. The acetylmuramic acid residues are substituted on their carbonyl groups by a tetrapeptide. These peptidoglycan strands are in turn cross-linked by a genus-specific pentapeptide from the dibasic amino acid (third residue from carboxyl end) to the terminal D-alanine residue in the tetrapeptide of the parallel peptidoglycan strand.[3] Therefore, cell wall synthesis is outlined as, 1) synthesis of the precursors of the cell wall, 2) the utilization of the precursors to form the linear peptidoglycan strands and 3) the cross-linking of these linear strands to make the two- or three-dimensional network which is the cell wall.

β-Lactam antibiotics act on the third stage of cell wall synthesis.[3] Penicillins and cephalosporins have been found to inhibit the enzymes needed in peptidoglycan cross-linking, a transpeptidase and/or a carboxypeptidase.[3] The peptidoglycan transpeptidase activity is known to cleave the peptide bond between the C-terminal dipeptide, D-ala-D-ala, of the pre-cross-linked peptidoglycan strands, and perform the coupling to the pentapeptide crosslinker. The carboxypeptidase activity removes a single terminal D-alanine residue; therefore, it functions to regulate the extent of cross-linking since removal of a terminal D-alanine prevents cross-linking of that peptide unit.[3] The reaction of a β-lactam with either enzyme results in the formation of a penicilloyl-enzyme, blocking the enzyme's active site, and therefore, preventing further cell wall synthesis.

Structural and Chemical Reactivity Features. In spite of the significance that β-lactams have in chemotherapy, little is known about the fundamental factors contributing to their antibiotic potency. However, it can be said that among the many possible factors which make a β-lactam effective one structural and one chemical feature is most typical: The molecular geometry should be such that the antibiotic will be mistakenly recognized by the transpeptidase enzyme as a normal substrate. On the other hand, its chemical reactivity should be significantly high in order to allow the acylation of the nucleophilic enzyme.[4,5]

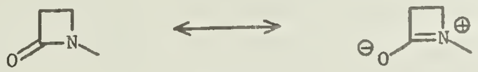
Strominger and coworkers[3] postulated from model conformational studies that because of their mimic of the dipeptide acyl-D-ala-D-ala, the bicyclic β-lactams, which are a L-D-dipeptide, are recognized as substrates by the transpeptidase. Their hypothesis is supported by the fact that pencillins and cephalosporins with substituted carboxyl groups are very poor inhibitors of the transpeptidase. A free carboxyl group in penicillins and cephalosporins either is essential for or greatly enhances antimicrobial activity. Therefore, if penicillin is a substrate analog of some structure in the peptidoglycan, its carboxyl group must be the analog of the carboxyl group in the terminal D-alanine residue, the only free carboxyl present.[3]

Using x-ray analysis of penicillins and studies of stereomodels, Lee[6] suggested that the strained conformation of the β-lactam represents the transition state configuration of the D-ala-D-ala residues in the active site of the transpeptidase. Since penicillins are already suitably distorted, their binding to the enzyme will be more favorable to the extent of not having to expend the energy for distortion. In fact, Boyd et al. has calculated that the substrate-enzyme interaction must supply 8.5 or 3 kcal to strain the peptide bond into a conformation similar to that of the β-lactam amide of penicillins and cephalosporins, respectively. Boyd (1977) had also computed that the tetrahedral adducts formed during nucleophilic attack by a hydroxyl ion on the carbonyl carbon of a R-Gly-Gly peptide are very similar to the antibiotic structure, if one assumes the attack to take place on the α-face of the molecule.[6]

Further support for a mimicry of D-ala-D-ala needed in the recognition by the peptides comes from the work of Nieto and coworkers.[7] In studying a series of tripeptides as inhibitors and substrates of Staphylococci sp. D,D-carboxypeptidases, they concluded that the C-terminal dipeptide (D-ala-D-ala) is the main portion of the molecule concerned with the initial binding to the enzyme surface. Although the alanine residues provide most of the free enthalpy of binding, the side chain characteristics of residue three can cause significant changes in V_{max} values.

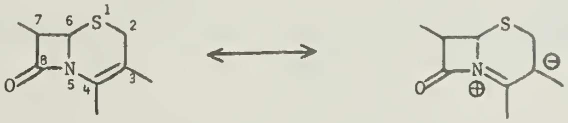
Although the above hypotheses appear attractive, their complete acceptability is hampered by the fact that 1) β-lactam antibiotics do not exhibit a particularly high affinity for their enzymes as expected for transition state analogs, 2) the β-lactam antibiotic, upon binding to the enzyme, must itself be activated into a transition state to become a powerful acylating agent. This transition state would be the one which might be common to antibiotic and substrate, but this would require the enzyme to supply more free energy to strain the amide bond further, and 3) the assumption that β-lactam antibiotic activity was not dependent on the nature of the side chains has been subsequently disproven.[7b]

The key to the chemical reactivity of the β-lactam antibiotics lies in the loss of resonance stabilization resulting from ring strain. In 1949, Woodward suggested that in a monocyclic β-lactam, normal amide resonance can occur which tends to shorten the C-N bond and lengthen the C-O bond. A principal requirement for maximization of this type of charge delocalization is that the three atoms connected to the nitrogen atom be coplanar with it so that the unshared electron pair of the nitrogen atom can be involved in π-bonding with the adjacent carbonyl atom.[4]



In order to study biological activity as a function of chemical reactivity of the β-lactam moiety of the antibiotics, Sweet and Dahl[8] studied the degree of amide resonance in penicillins and cephalosporins through x-ray bond length calculations and IR carbonyl stretching frequencies. X-ray data indicated that biologically active penicillins have a longer N-CO bond length than unstrained β-lactams as well as a shorter C=O bond length. Another significant feature seen in the x-ray studies was the distance the N-atom is displaced from the plane designated by its three substituents (∿0.40Å). This lack of planarity reduces β-lactam resonance stabilization and contributes significantly to the decreased β-lactam stability.[8] Reduction in electron delocalization is also indicated from the shift in carbonyl stretching frequency of β-lactam antibiotics. The infrared absorption band increases from ∿1750 to 1780 cm^{-1} as the planarity of the N-atom decreases, indicating an accompanying increase in double bond character between the C- and O-atoms.[8]

In cephalosporins, lability of the amide bond can also be attributed to possible enamine resonance along with the lack of planarity.[8] Enamine resonance may arise from the delocalization of the N-atom's unshared electron pair into the adjacent olefinic π-orbitals. Biologically active cephalosporins indicated a shift in bond lengths C(3)-C(4) and C(4)-C(5).



The double bond length of 1.360Å in the dihydrothiazine ring was a bit longer while the single bond adjacent to it [C(4)-N(5)], of length 1.393Å was a bit shorter than the expected values of 1.330Å and 1.470Å respectively.[8] The shift in bond lengths indicated the existence of the electron delocalization in the N-C=C system, and therefore, a contribution to the decrease in cephalosporin amide resonance.

In his analysis of the biologically inactive Δ^2-cephalosporins, Sweet[8] stated that the amide N-atom in the β-lactam ring has approximately the planar trigonal character commonly found in free amides with the N-atom lying only 0.06Å from the plane of its three substituents. All bond lengths and the carbonyl stretching frequency were reflective of a planar β-lactam ring. Therefore, by effecting amide resonance, the geometry of the β-lactam ring seems to govern the chemical reactivity and consequently biological activity of the β-lactam antibiotics.

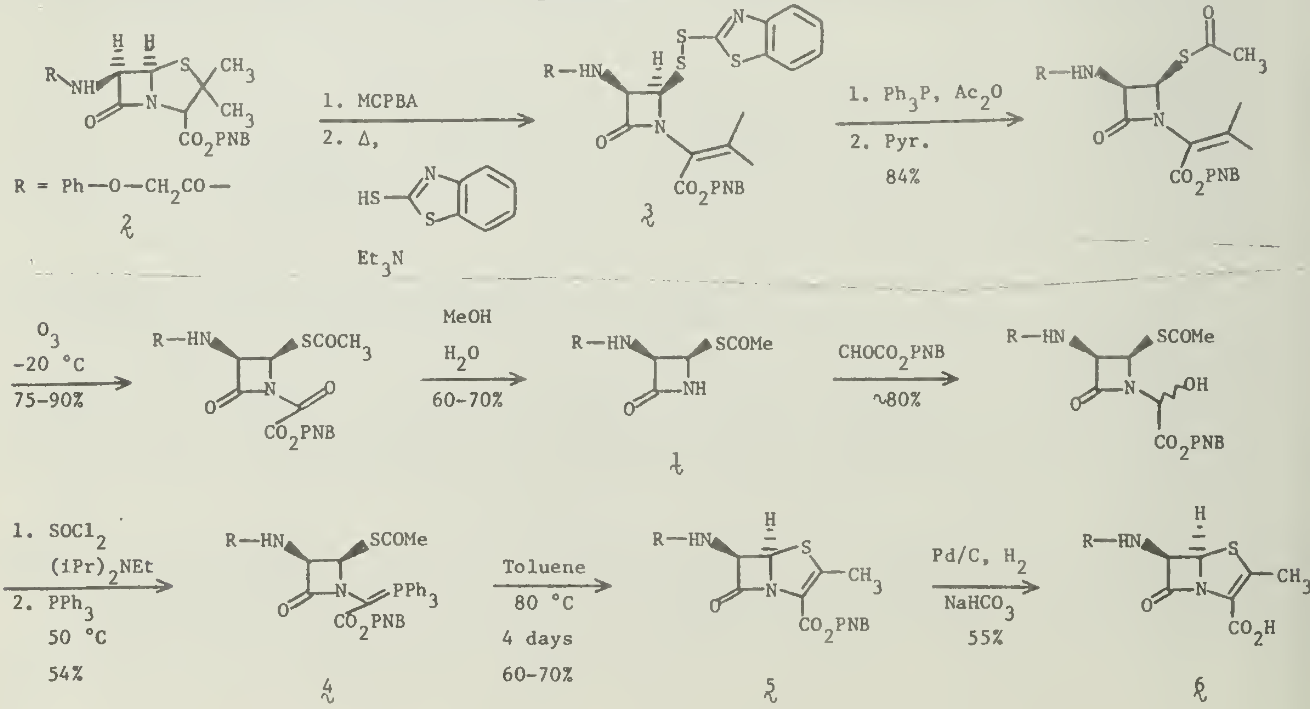
Using extended Hückel MO calculations to calculate charge distributions in the β-lactam ring of model nuclei of cephalosporins and penicillins, Boyd[9] was able to corroborate Sweet's findings. Boyd showed that there was an increased positive charge on the carbonyl carbon of the 3-cephem and penam biologically active nuclei compared to the biologically inactive 2-cephem and cepham nuclei, and concluded that increased reactivity results from increased susceptibility to nucleophilic attack.

Compound permeability of the cell wall and affinity for the enzyme active site both contribute to biological activity of β-lactams.[4] However, little is understood regarding these components, consequently no discussion will be presented.

Penem Synthesis. In 1977, Woodward proposed a chemically reactive β-lactam, a penem, that could possibly combine both the reactivity and biological activity of cephalosporins and penicillins.[10,11] His synthetic analysis of this novel β-lactam nucleus envisioned the 4-acylthio-2-azetidinone 1 as the key intermediate. The basic premise was to develop methodology to allow preparation of a range of structures for structure-activity studies.

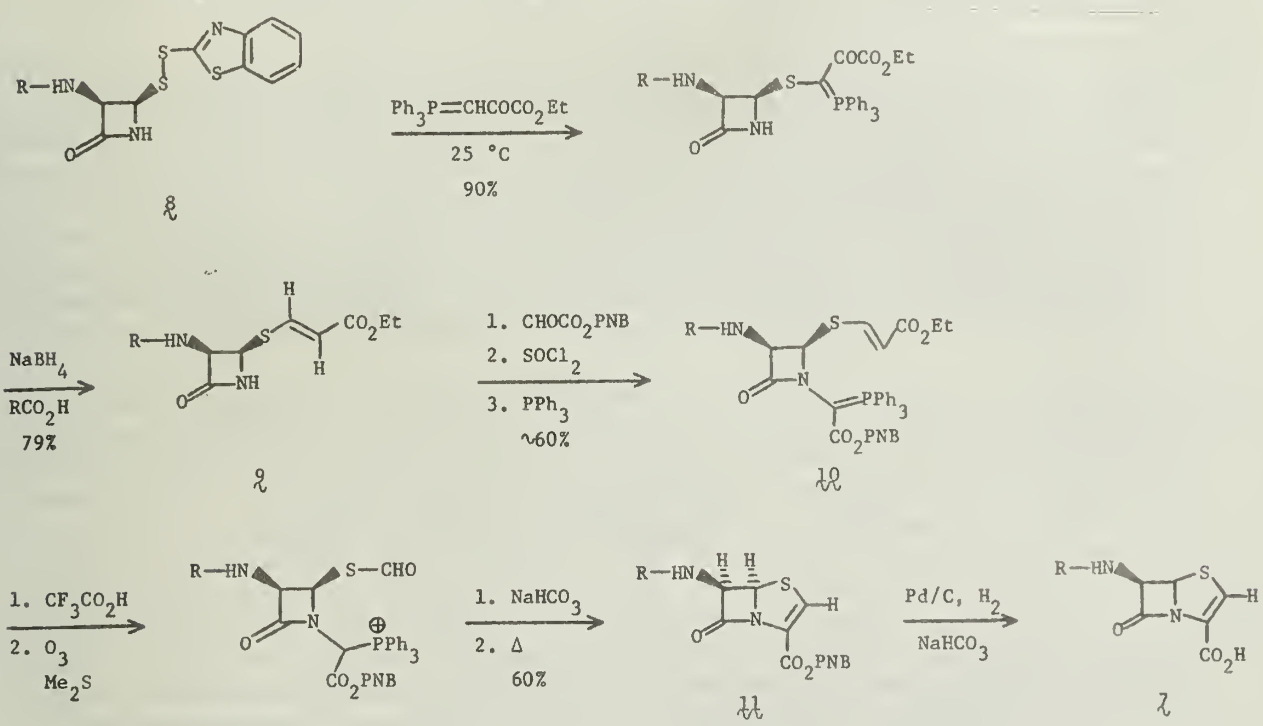
The intermediate 1 was prepared using Penicillin V 2 as optically active starting material followed by interception of the rearrangement equilibrium to give the disulfide 3. Reductive acylation of the disulfide followed by ozonolysis and methanolysis gave the desired intermediate 1. Condensation with glyoxilic ester and phosphorane formation to give 4 set up the intramolecular Wittig reaction to form the thiazoline ring. With the p-nitrobenzyl ester the Wittig reaction proceeded well to give the penem 5. Cleavage of the p-nitrobenzyl ester gave the desired penem acid 6.

Scheme 1



The 2-unsubstituted penem-3-carboxylate **7** was prepared proceeding from the intermediate **8** obtained similarly to intermediate **1**.[11] The disulfide **8** was reductively acylated then reduced with $NaBH_4$ to give the azetidinonyl thioacrylate **9**. This thioacrylate was transformed into the phosphorane **10** as previously seen in Scheme I. Ozonolysis under acidic conditions to protect the phosphorane followed by neutralization with $NaHCO_3$ gave the phosphorane which spontaneously closed to the penem **11**.[11]

Scheme 2

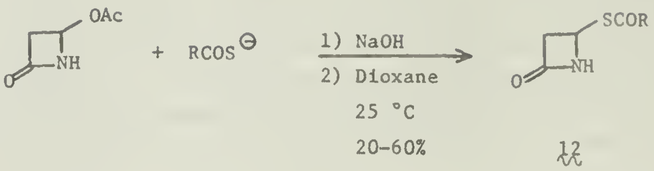


Instability to acids was a characteristic feature of the new penem system. Even traces of acids (HCl, TFA, formic acid) induced decomposition to thiazole-4-carboxylates.[11]

Decision to construct the 6-unsubstituted members of the penem system was made because it was believed that the fundamental chemistry of the new system could be best explored with simple representatives.[14] In effect, to reduce the problem to its simplest form by removing any effects from secondary structure.

Work done by Clauss, Grimm and Prossel,[12] in which they showed that the acetoxy group of 4-acetoxy-2-azetidinones could be displaced by nucleophiles, laid the bases for the unsubstituted series. Using this procedure, Woodward and coworkers prepared the thioanalogues **12** by displacement with various thiocarboxylates under basic conditions.[13] Elaboration

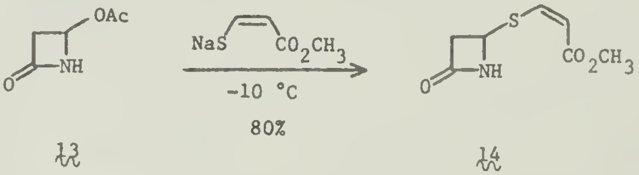
Scheme 3



of the thiazoline ring followed the sequence outlined for the 6-substituted penems in Scheme I.

In order to study the effects of stereochemistry on biological activity, the racemic penem-3-carboxylic acid as well as the enantiomers were prepared.[14,15] Because of the instability of the 4-formylthio-2-azetidinone, a β-mercaptoacrylate 14 was preferred as an intermediate to the racemic penem.[15] The azetidinone 14 was prepared from the 4-acetoxy-β-lactam 13 through a displacement reaction using the sodium salt of methyl-cis-β-mercaptoacrylate in aqueous solution. Elaboration of 14 to the racemic penem followed the procedures used for lactam 9 in Scheme II.[15] Using the chiral β-mercaptoacrylate ester of (-)-menthol the enantiomers were prepared following the

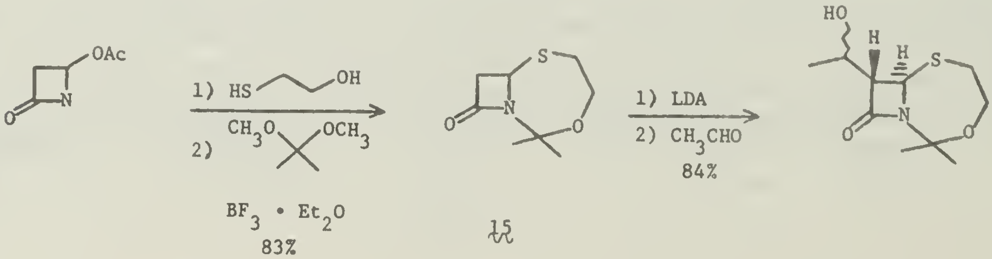
Scheme 4



reaction sequence used in preparation of the racemate. Enantiomer separation by fractional crystallization occurred after acetoxy displacement with the chiral thioacrylate salt.[15]

The influence of the side chain at C-6 of the penem was also investigated.[18] Previous work had already produced the 6-acylamino penem carboxylic acids.[10,11] Wishing to introduce the α-hydroxyethyl side chain known to enhance antibacterial potency of thienamycin,[17,18] Pfaendler and coworkers[16] utilized a known aldol type reaction. The novel bicyclic lactam 15 was used as the key intermediate. The intermediate was condensed with

Scheme 5



acetaldehyde to give the epimeric mixture of alcohols which were separated by crystallization after aminoketal hydrolysis. Displacement of the sulfone with *cis*-β-mercaptoacrylate and elaboration to the desired penems was identical to that for the racemic penem.[16]

To date, several other synthesis of penem carboxylic acids have been accomplished.[19,20] However, none of the other approaches have demonstrated the generality of the Woodward approach.

Penem Structure-Activity Study. The simplest of the biologically active penems (2,6-unsubstituted penemcarboxylic acid) was studied using the criteria of Sweet and Dahl[8] for structural, chemical and biological activity.[5] The penem system, active against *S. aureas*, *E. coli* and *P. aeruginosa* showed a departure from coplanarity of the β-lactam N-atom of 0.42Å with a OC-N bond length of 1.419Å and N-C bond length of 1.427Å. The penem carbonyl stretching frequency was 1798 cm^{-1}. This physical data indicates a low degree of amide resonance yet a weaker enamine resonance compared to cephalosporins. Hydrolysis studies on the penem system showed it to have a half life of 20 hrs. Therefore, high chemical reactivity of the β-lactam and pyramidal geometry of the β-lactam nitrogen proved sufficient prerequisites for antibiotic activity for the penem class of β-lactams.[5]

When studying the penems' biological activity against the Gram-positive and Gram-negative bacteria, the following structural activity correlations can be made. In general, the penems are at least twice as active against Gram-positive bacteria as against Gram-negative bacteria and are at least comparable to penicillins and cephalosporins. The 5R penem is twice as active as the racemic compound while the 5S penem is totally inactive. The 6-acylamino penem proved to be much less active than the 6-unsubstituted penem. Yet, the threo-6-hydroxyethyl penem was at least twice as active against the Gram-positive bacteria as the other penems but showed comparatively low activity against Gram-negative bacteria. The erythro-6-hydroxyethyl penem showed poor activity against all bacteria.

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ORTHO LITHIATIONS OF BENZONITRILES

Reported by Timothy D. Krizan April 5, 1982

A common approach to the synthesis of functionalized aromatic compounds is ortho lithiation directed by substituents on the ring.[1] The many known ortho directing substituents share one common structural feature: the presence of a heteroatom with a lone pair (e.g., O,S,N,F or Cl). The resulting aryllithium species react with electrophiles to incorporate a variety of functional groups.

Two major factors appear to contribute to the ability of the substituent to direct lithiation regioselectively. The first, chelation with the alkyllithium reagent by the lone pairs on the substituent,[2] is best demonstrated by the regiospecific, high yield lithiation of N,N-dimethylbenzylamine.[3] The proton at the 2-position would be expected to be the least acidic, due to electron releasing effects of the benzylic methylene group, yet it is specifically abstracted by n-BuLi. Chelation has been shown to stabilize the lithiated substrate.[4]

The second factor, an inductive effect of the substituent which increases the acidity at the ortho position,[1] is demonstrated in the lithiation of 4-methoxy-N,N-dimethylbenzylamine.[5] When n-BuLi alone is used, the proton ortho to the amine is specifically abstracted, indicating the importance of chelation. When n-BuLi with tetramethylethylenediamine (TMEDA) is used, the kinetic basicity of the alkyllithium is increased and the proton ortho to methoxy is selectively removed.

Inter- and intramolecular competition studies have been used to rank the relative directing abilities of various substituents.[5,6] Up to this point, it has been impossible to correlate the competition rankings with any electronic substituent parameters, even qualitatively. It is apparent from the rankings that the best ortho directors have both high chelation and high inductive electron withdrawing abilities.

The 2-bromo derivatives of benzoic acid,[7] methyl benzoate,[8] and benzonitrile[9] have been shown to undergo halogen-metal exchange to generate 2-lithiobenzoic acid equivalents. Similar equivalents have been generated by directed ortho lithiation of primary[10] and secondary[11] benzamides, aryl oxazolines[12], esters[13], and N,N-dimethylhydrazones of benzaldehydes.[14] The only benzonitrile reported to undergo ortho lithiation is 3-chlorobenzonitrile[1], for which a chelation between the lithium reagent and the chlorine can be plausibly invoked. In these laboratories, it has been demonstrated that the cyano group can direct ortho lithiation unaided by other substituents.[15] In this seminar, evidence will be presented which suggests that chelation effects are negligible in these cases.

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THE CHEMISTRY OF SAXITOXIN

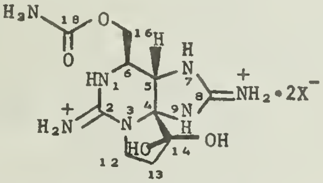
Reported by Eric Weber April 8, 1982

Introduction

Saxitoxin (STX), a marine toxin which has been isolated from a variety of shellfish,[1] is one of the most toxic nonprotein poisons known to man. Experimental data suggest that a single dose of 0.2-1.0 mg would prove fatal to a human. STX is produced by certain dinoflagellates, unicellular organisms which, under the proper conditions, grow so quickly that the water is discolored, hence the term "red tide". Shellfish feeding on the dinoflagellates at this time have caused serious human and animal poisoning.[2]

Structure Determination

In the last twenty years at least six different structures of STX have appeared in the literature.[3] It was not until 1975 that crystalline derivatives suitable for x-ray crystallography studies could be obtained.[4] The results of these analyses, together with data from ^{13}C NMR[4a] and ^{1}H NMR studies,[3c] led to the conclusive structure determination of STX. Structure 1 is now the accepted structure of STX.



The crystal structure shows that the five-membered ring containing the guanidine group is planar with a maximum deviation from the least-squares plane of 0.001 Å. In addition, four (N-3, C-4, C-12, and C-13) of the five atoms in the other five-membered ring form a plane with a deviation of 0.01 Å, while C-14 is out of the plane by 0.62 Å. Four atoms of the six-membered ring are also planar. Atoms N-3, C-4, C-5, and C-6 form a four atom plane with a maximum deviation of 0.001 Å. Atoms N-1 and C-2 are 0.87 Å and 0.57 Å from this plane, respectively, both being on the same side. The crystal structure indicates that the $-CH_2OCONH_2$ fragment at C-6 adopts a pseudo-axial configuration.[4b]

Recent ^{1}H-NMR studies by Shimizu[5] and Niccolai[6] suggest that the conformation of STX in solution is nearly identical to that in its crystalline state.

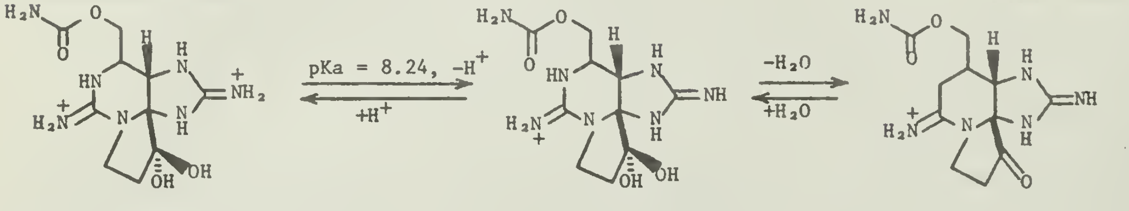
STX has been determined to have two pKa values of 8.24 and 11.60. The source of the lower pKa has been the center of much debate in previous years.[2,3c,4a,8] Recently Shimizu[5] was able to establish the source of this second pKa. Upon increasing pH, Shimizu observed changes in the chemical shifts of several of the protons in the ^{1}H NMR spectrum of STX. The change in chemical shift was greatest for the protons attached to C-5, and the pH at which the largest change was observed coincided with the pKa. Assuming that protons on a carbon attached directly to a dissociating moiety will be most influenced by a change in the pH, the imidazole guanidine group was determined to be the origin of the pKa of 8.4.

Since the rate of interconversion between the keto and hydrate forms of STX is slow on the NMR time scale, Shimizu[5] has been able to determine the percent population of the different forms of STX at varying pH (Table I). The ratios of the total single charged species were calculated using the Henderson-Hasselbach equation.

Table I

form (no. of charge)	pH 4.8	pH 7.7	pH 8.4	pH 9.8
keto (+1)	0	1	24	36
hydrated (+1)	0	23	37	62
hydrated (+2)	100	76	39	2

Within the pH range of 7.0-8.0 there exist in equilibrium three forms of STX: the bivalent cationic hydrate, the univalent cationic hydrate, and the univalent keto form (Eqn. 1).

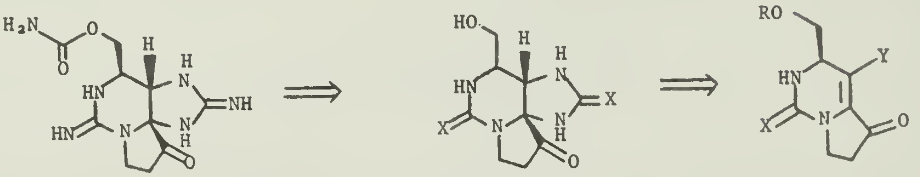


(1)

Synthesis

In 1977 Kishi[9] reported the total synthesis of STX. Part of his retrosynthetic analysis is depicted in Scheme I.

Scheme I

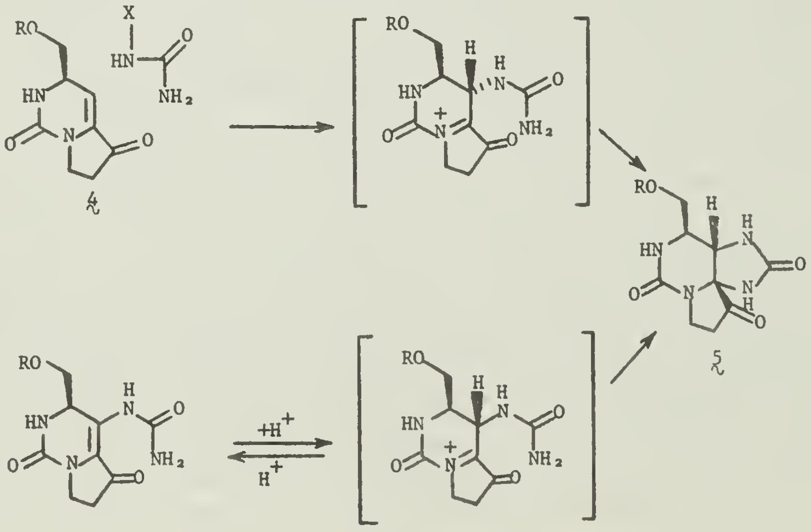


2, X=O or S

3

Kishi felt it was important to introduce the guanidino groups late in the synthesis, so as to avoid technical difficulties in the handling of the guanidine derivatives. He proposed two possibilities for the cyclization of 3 → 2 (Scheme II).

Scheme II



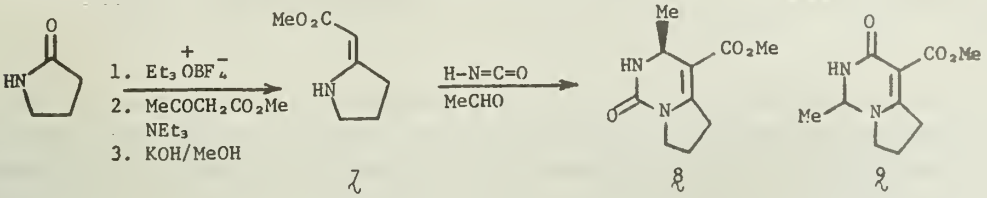
4

5

6

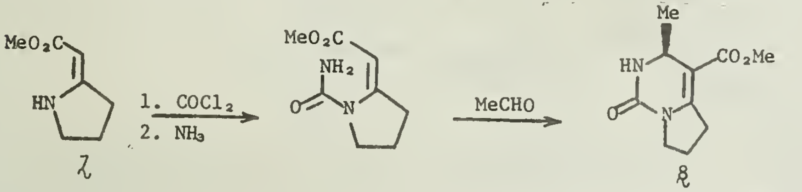
For the first possibility in Scheme II, it was believed that the aminating reagent would approach 4 from its α-face, due to steric control. Subsequent cyclization would afford 5 with the proper stereochemistry at C-4 and C-5. The second possibility for cyclization depended upon rapid protenation-deprotenation of 6, followed by slow cyclization.

The retrosynthetic analysis was first tested in the 14,16-deoxo series.[9b] Using a modified Eschenmoser procedure,[10] 2-pyrrolidinone could be converted to the vinylogous urethane 7 (Eqn. 2). Reaction of 7 with acetaldehyde and isocyanic acid afforded one product whose spectroscopic data were in agreement with the desired urea ester 8. The spectroscopic data did not conclusively eliminate formation of the alternative product 9.



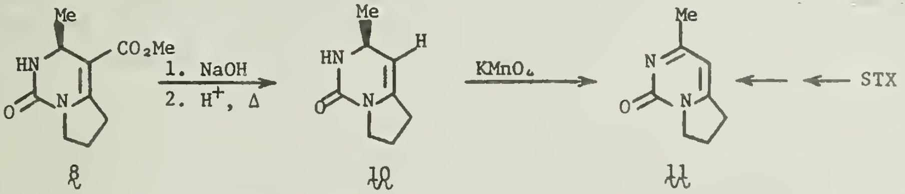
(2)

To verify the structure of the product, the urea ester 8 was synthesized via a two step reaction precluding the formation of 9 (Eqn. 3).[9b]



(3)

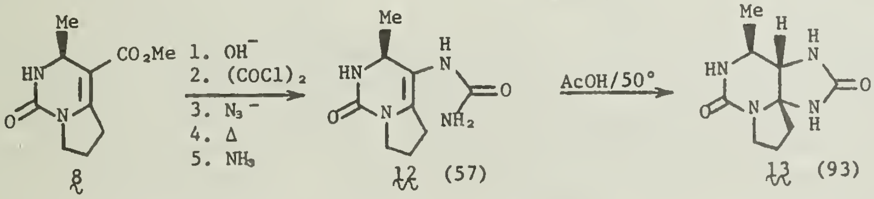
The urea ester obtained was identical with the product previously isolated. The formation of 8 in eqn. 2 was also supported by the observation that saponification, decarboxylation, and oxidation ($KMnO_4$) of 8 afforded the urea 11, which is a known degradation product of STX (Eqn. 4).[11]



(4)

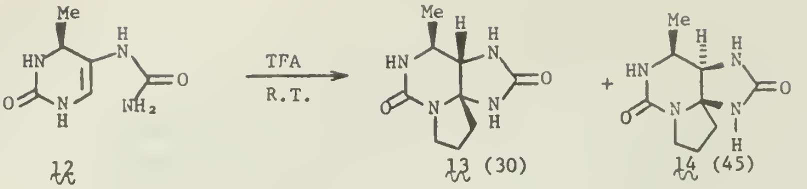
It was at this point that the first possibility for cyclization, offered in Scheme II, was determined to be impractical due to the observed lability of the urea 10. The investigators turned their attention to the second possibility for cyclization.

Saponification of the urea ester 8, followed by treatment with oxayl chloride, afforded the acid chloride (Eqn. 5). Subsequent reaction with sodium azide and heating, which effected the Curtius rearrangement, followed by amination with ammonia, gave the bicyclic urea 12 in excellent overall yield. Cyclization of the bicyclic urea 12 to the tricyclic urea 13 was found to proceed smoothly in acetic acid at 50°C.[9b]



(5)

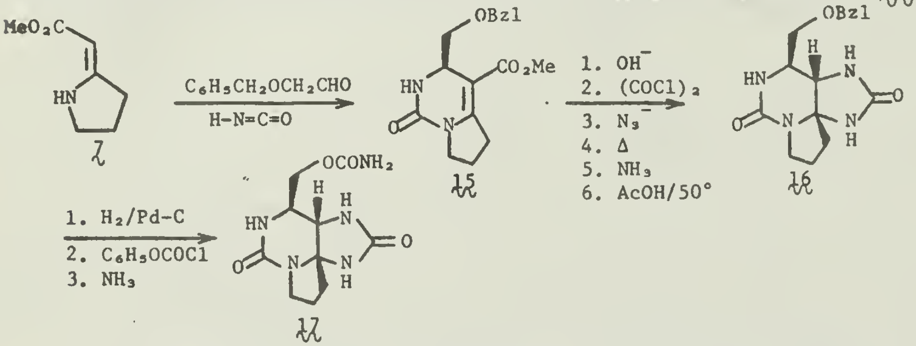
The ^{1}H NMR spectrum of the tri-N-methyl derivative of 13 showed the coupling constant between the C-5 and C-6 proton to be 1.0 Hz, which was close to that of STX (1.3 Hz).[3c] Further evidence for the stereochemistry of 13 was the observation that cyclization of 12 in neat trifluoroacetic acid at room temperature resulted in two tricyclic ureas 13 and 14 (Eqn. 6). The coupling constant between the C-5 and C-6 protons of the tri-N-methyl derivative of 14 was found to be 3.5 Hz.[9b]



(6)

The next goal was the introduction of the carbamate functionality at the C-1 position.

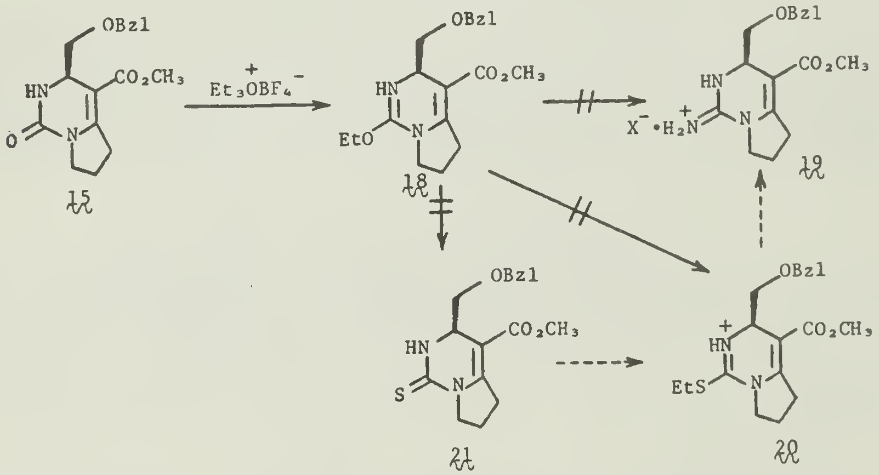
Reaction of the vinylogous urethane 7 with benzyloxyacetaldehyde in the presence of isocyanic acid resulted in the expected urea ester 15 (Eqn. 7). Conversion of 15 to the tricyclic urea 16 was accomplished using methodology previously described. Removal of the benzyl group followed by carbamylation of the alcohol proceeded smoothly to give the tricyclic urea 17.[9c]



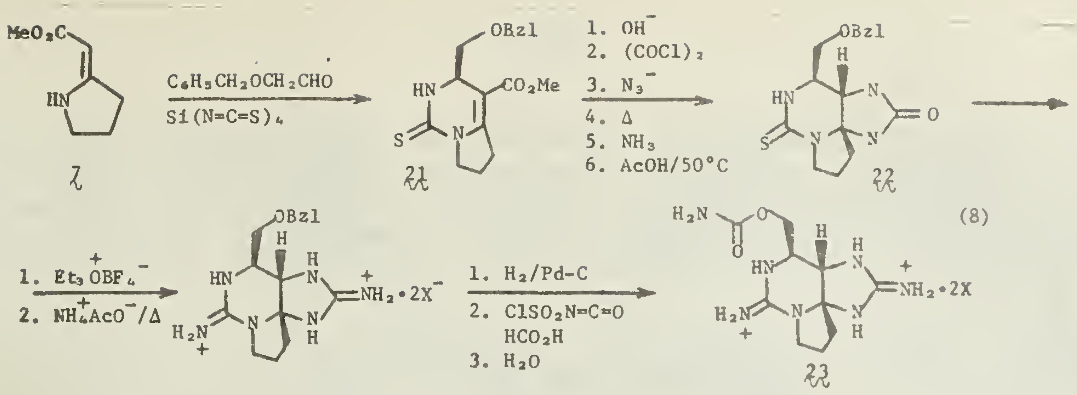
(7)

With regard to functionality at C-2 and C-8, model studies indicated that it would not be possible to transform the iminoether 18 to the guanidine 19 or the thioiminoether 20 (Scheme III). However, it was found that the thiourea

Scheme III

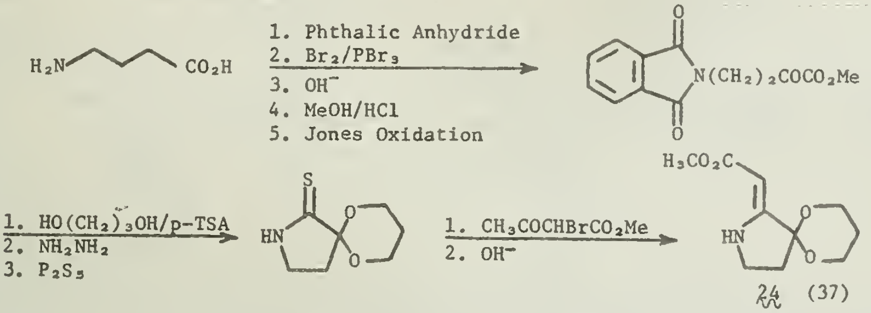


ester 21 could be prepared directly from the vinylogous urea 7 by reaction with benzyloxyacetaldehyde and silicon tetraisothiocyanate (Eqn. 8).[12] Cyclization of 21 to the expected tricyclicthiourea 22 proceeded in good yield. The simultaneous introduction of functionality at C-2 and C-8 could be realized by treatment with triethyloxonium tetrafluoroborate and ammonium acetate. Removal of the benzyl group and treatment of the resulting alcohol with chlorosulfonyl isocyanate afforded 12-deoxosaxitoxin 23.[9c]



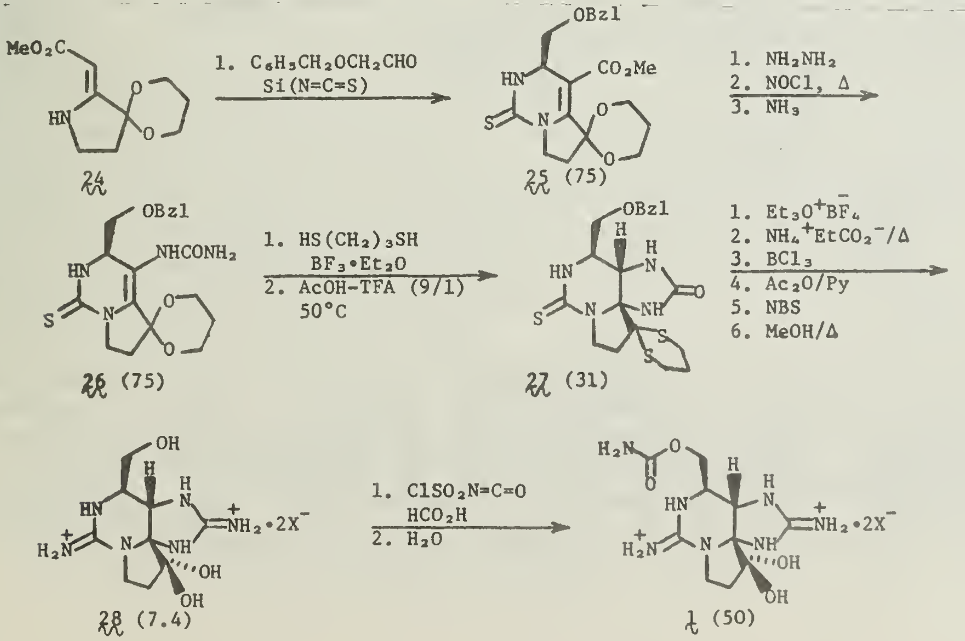
(8)

The extension of this methodology to precursors, which would allow for proper functionalization at the C-12 position, now remained in order to complete the total synthesis of STX. The vinylogous urethane 24 was prepared according to the method outlined in eqn. 9.[9a]



(9)

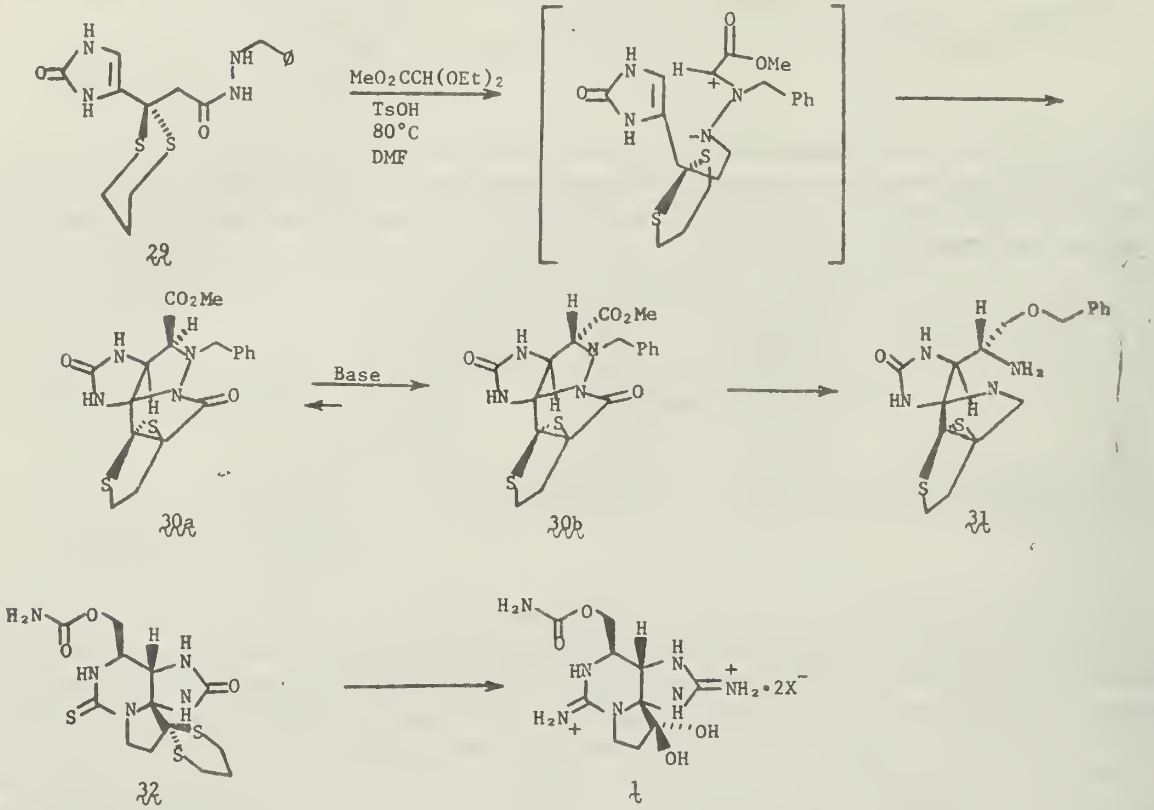
Conversion of 24 to the thiourea 25 was accomplished using the established method (Eqn. 10). The methyl ester of 25 could only be hydrolyzed under vigorous conditions, which led to decreased yields. However, the transformation of 25 to 26 could be effected in reasonable yield by treatment of 34 with hydrazine, followed by nitrosyl chloride oxidation. It was necessary to convert the ketal 26 to the thioketal before cyclization, since 26 was labile under acidic conditions. Cyclization of the thioketal to the desired tetracyclicurea 27 was made possible with a mixture of acetic and trifluoroacetic acids (9/1). Transformation of 27 to the bisguanidine 28 was accomplished using methods developed in the 14-deoxo series. After complete acetylation, the thioketal group was hydrolized by reaction with NBS in aqueous acetonitrile. Finally, the acetyl group was removed in refluxing methanol to afford the penultimate bisguanidine 28 and carbamoylation yielded STX 1.[9a]



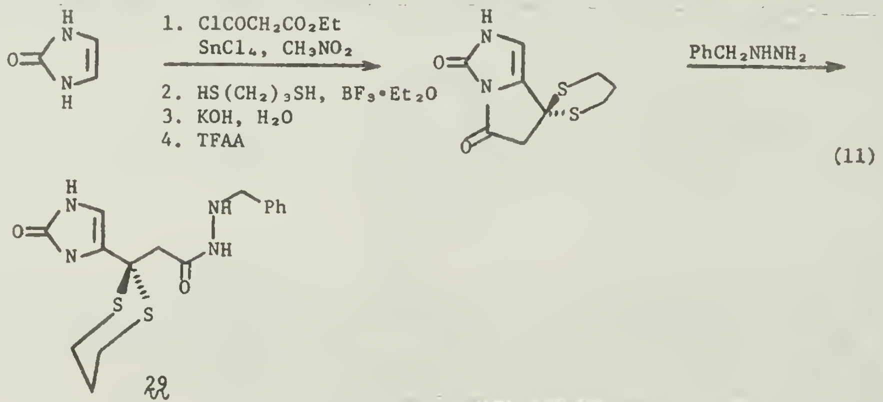
(10)

This past year Jacobi[13] has undertaken the total synthesis of STX from a different approach. He was able to synthesize a key intermediate 29, which has the proper stereochemistry at the 4-, 5-, and 6-positions via an intramolecular 1,3-dipolar addition of an azomethine imine (Scheme IV).[14] Jacobi notes that there is ample precedence for the reductive cleavage of 30b to 31[15] and the transformation of 32 to 1.[9a]

Scheme IV



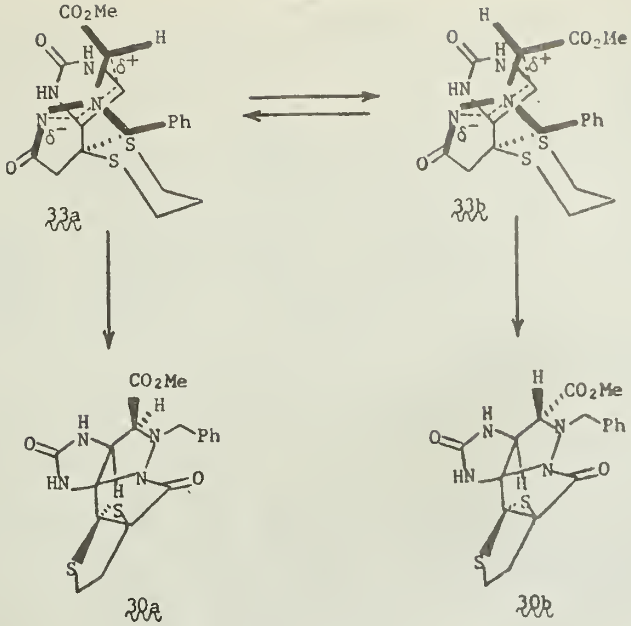
The synthesis of the required hydrazide 29 is outlined in Eqn. 11.[13]



(11)

A comparison of the two transition states for the cyclization offers an explanation for the observed stereoselectivity (Scheme V). There is severe nonbonded interaction between the methyl ester and the benzyl group in the transition state 33b. Under conditions of kinetic control, the formation of adduct 30a is favored. However, upon equilibration, adduct 30b predominates. Jacobi reports isolating only 2% of the adduct 30a after equilibration.

Scheme V



Biological activity

STX is a neurotoxin whose only known pharmacological action is its remarkable specific blocking of sodium channels in nervous membranes.[16] The free flow of sodium through these channels is essential for the conduction of nerve impulses.[17] Equilibrium and rate kinetic experiments indicate that one molecule of STX binds reversibly with one sodium channel to produce the blocking action.[18]

In 1965, Kao and Nishiyama[19] were the first to propose that the imidazole guanidine moiety was entering the sodium channel first, and then becoming lodged due to the rest of the molecule being too large to pass through the channel. Studies by Hille[20] on the permeability of the sodium channel to a number of organic cations and more recently the conclusive structure determination of STX, has led to a refinement of Kao's original proposal. Hille proposes that near the mouth of the sodium channel lies a selectivity-filter, approximately 3 by 5 Å in cross-section, into which the immidazole guanidine group can insert. The filter is thought to be lined with six oxygen atoms, with one pair assumed to be an ionized carboxylic acid. Thus, hydrogen bonding and electrostatic interactions could stabilize the binding complex. The channel above the selectivity-filter, which must accommodate the remaining portion of the STX molecule, is believed to have a cross-section of 9 by 10 Å. This model implies that when the imidazole guanidine group is inserted into the selectivity-filter, the planar pyridinium guanidine moiety and one of the hydroxyl groups of the C-14 carbon rests against the filter. This arrangement allows for both guanidine groups to be in close contact with the negative charge of the filter. At this time, it is unclear what role the unusually electropositive center at the C-14 carbon plays in this binding complex.

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MODERN METHODS OF 1,2 AND 1,3 CARBONYL TRANSPOSITIONS

Reported by Todd Jones April 12, 1982

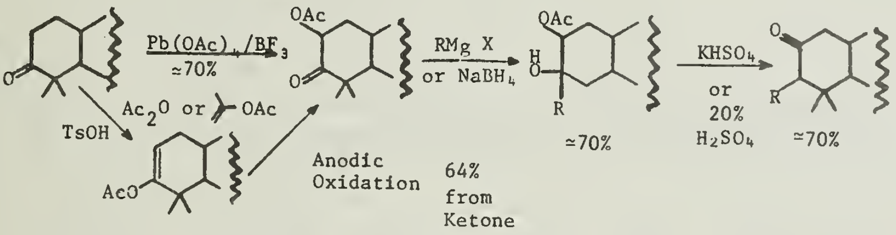
The carbonyl group plays a pivotal role in organic synthesis, and its importance is widely recognized.[1] Because of the many reactions associated with a carbonyl, it often is necessary and desirable to relocate it within a molecule. Shifting the carbonyl group to an α or β carbon constitutes a carbonyl transposition.

Evans[2] designates a carbonyl group as an 'E' group with the charge affinity pattern shown below. A 1,2 transposition of a carbonyl on a carbon skeleton

$$\overset{(-)}{C} - \overset{(+)}{C} - \overset{(-)}{C} - \overset{(+)}{C} - E$$

imposes a charge affinity inversion on the skeleton. A 1,3 transposition does not alter the charge affinity pattern, but it does relocate the primary center of reactivity. Many methods are available to transpose carbonyl groups. This abstract will selectively illustrate the most general methods[3] with emphasis on recent examples.

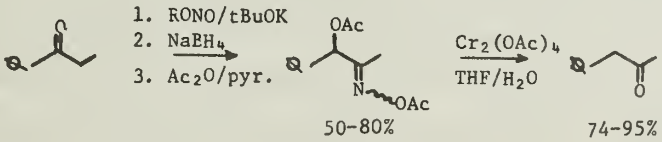
1,2 Carbonyl Transpositions: Oxidative α Substitution with Oxygen. Direct acetoxylation of a ketone may be accomplished by two general methods. One method is direct oxidation of a ketone with lead tetraacetate/boron trifluoride,[4a] and the second uses anodic oxidation of an O-acetyl enol ether in acetic acid.[4b,c,d] The resulting α-acetoxy ketone can be alkylated with a Grignard reagent or reduced with sodium borohydride to produce a vicinal acetoxy alcohol. Treatment with acid catalyzes a dehydration and hydrolysis to yield the transposed ketone.[4b] (Eqn. 1)



(1)

A variation of the above method is the oxidation of a trimethylsilyl enol ether with lead tetrabenzoate to yield an α-benzoyloxy ketone.[4e]

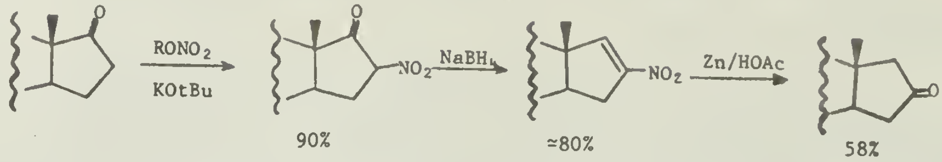
With Nitrogen. Nitration and oximination introduce oxidized nitrogen groups α to a carbonyl. Oximination is usually performed by addition of an alkyl nitrite to a ketone in basic medium.[5a] The resulting keto-oxime can be reduced and hydrolyzed to the transposed ketone. Corey[5b] has improved this process by reduction with sodium borohydride, acetylation of the alcohol oxime and finally reductive deoximation with chromous acetate. (Eqn. 2)



(2)

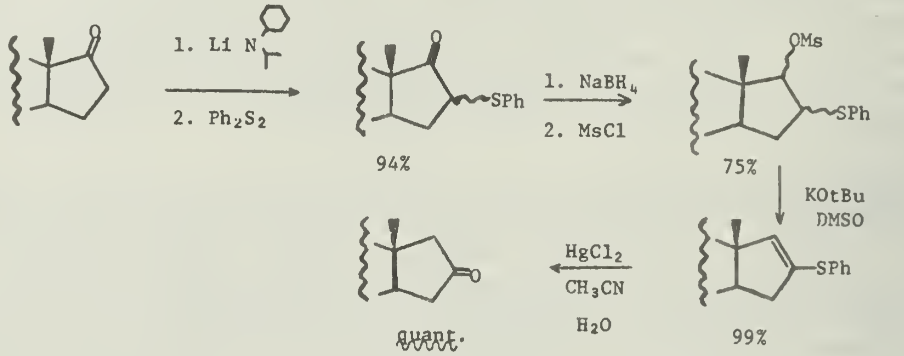
Nitration can be accomplished by adding an alkyl nitrate to an enolate.[5c] The nitroketone is subsequently reduced with sodium borohydride to produce a nitroolefin. The elimination of water in this sequence is often difficult.

The nitro group is reduced with zinc in acetic acid to provide the ketone. (Eqn. 3



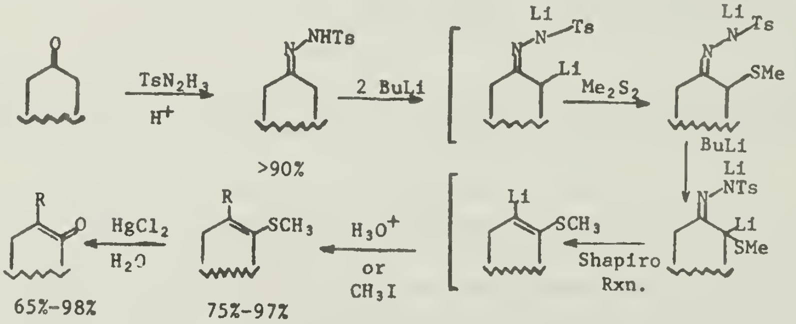
(3)

With Sulfur. Current research on carbonyl transpositions has centered around methods employing sulfur. Two basic approaches have been taken. Trost[6a] has demonstrated that treatment of a ketone with lithium N-cyclohexyl-N-isopropyl amide in tetrahydrofuran at low temperature followed by trapping with diphenyldisulfide leads to an α-sulfenyl ketone. Reduction of the ketone with sodium borohydride, followed by mesylation and base catalyzed elimination yields a vinyl sulfide. The vinyl sulfide may be hydrolyzed in high yield in the presence of mercuric chloride to give the transposed ketone. (Eqn. 4)



(4)

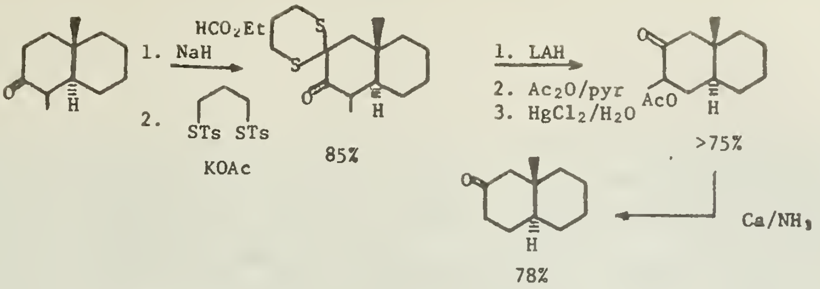
An alternate route to the vinyl sulfide was simultaneously demonstrated by Nakai and Kano, et. al.[6b,c,d] The tosylhydrazone of a ketone is subjected to two equivalents of n-butyllithium. The resulting dianion is sulfenylated with one equivalent of dimethyl disulfide. An additional equivalent of n-butyllithium is then added and the reaction mixture is warmed to induce a Shapiro[6e] reaction. The anion is quenched with a proton source. (Eqn. 5)



(5)

This sequence is regioselective. The proton removed from the α carbon is usually syn to the tosylhydrazone. If a geometrically pure tosylhydrazone is used, the carbonyl will regioselectively be transposed to the syn α carbon, depending on the base and solvent system used.[6c,d] This method can also be alkylative, by quenching the Shapiro reaction product with an alkylating agent.[6b]

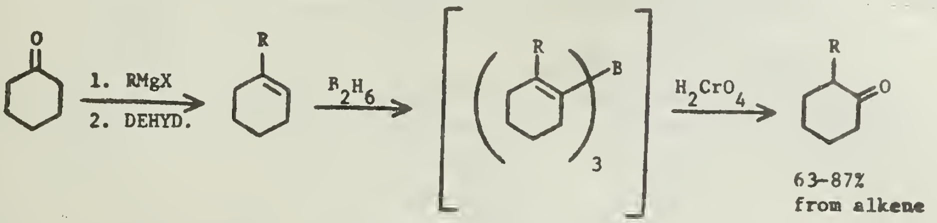
Another approach using sulfenylation was introduced by Marshall.[6f] The hydroxymethylene derivative of a ketone affords a thioketal ketone upon treatment with 1,3 propanedithiol di-p-toluene sulfonate and potassium acetate in ethanol. Reduction of the ketone with lithium aluminum hydride followed by acetylation and hydrolysis in the presence of mercuric chloride yields an α-acetoxy ketone. A calcium/ammonia reduction affords the transposed ketone. (Eqn. 6)



(6)

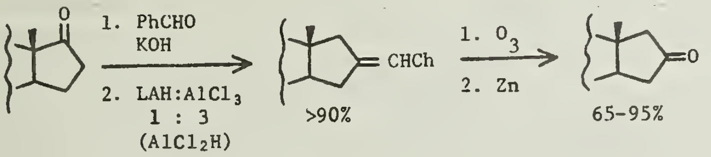
Non-Oxidative α Substitution:

Hydroboration. Brown[7] has reported an alkylative transposition using hydroboration. A ketone is alkylated with a Grignard reagent and dehydrated. The resulting alkene is hydroborated and then oxidized with chromic acid to yield a transposed ketone. (Eqn. 7)



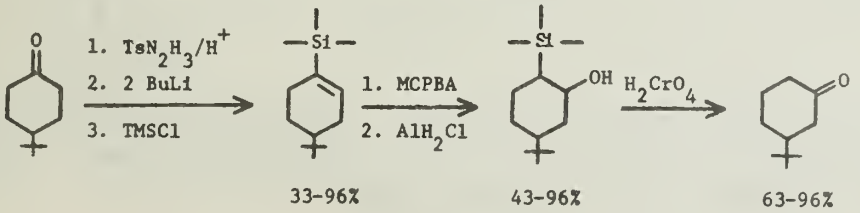
(7)

Benzylidenation. Meakins, et. al.[8] has shown that benzylidenation of a ketone followed by reduction and ozonolysis is a useful ketone transposition. (Eqn. 8)



(8)

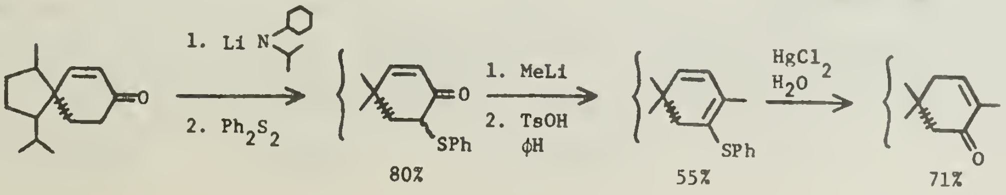
Vinyl Silanes. Paquette[9] demonstrated a novel method of ketone transposition. A ketone is converted into a tosylhydrazone and treated with butyl lithium to induce the Shapiro reaction.[6e] The resulting vinyl anion is trapped with trimethylsilyl chloride to produce a vinyl silane. The vinyl silane is epoxidized with m-chloroperbenzoic acid and reduced with chloroalane. The resulting alcohol is oxidized to yield the transposed ketone. (Eqn. 9)



(9)

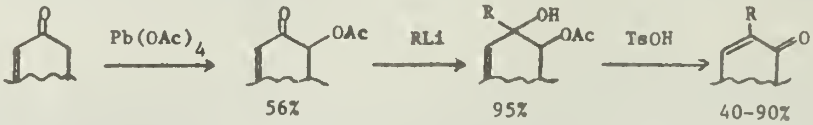
1,2 Enone Transposition.

Unsaturated ketones can also be transposed. Trost's[10a] sulfenylation method has been extended to enones. (Eqn. 10) This transposition was essential in Trost's synthesis of Acorenone B.



(10)

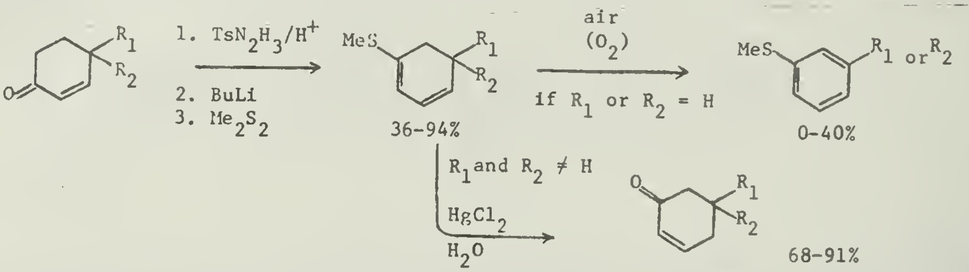
The same transformation may be achieved by acetoxylation as shown by Oppolzer.[10b] Treatment with lead tetraacetate followed by alkylation and acid yields the transposed enone. (Eqn. 11) The acid catalyzed dehydration is



(11)

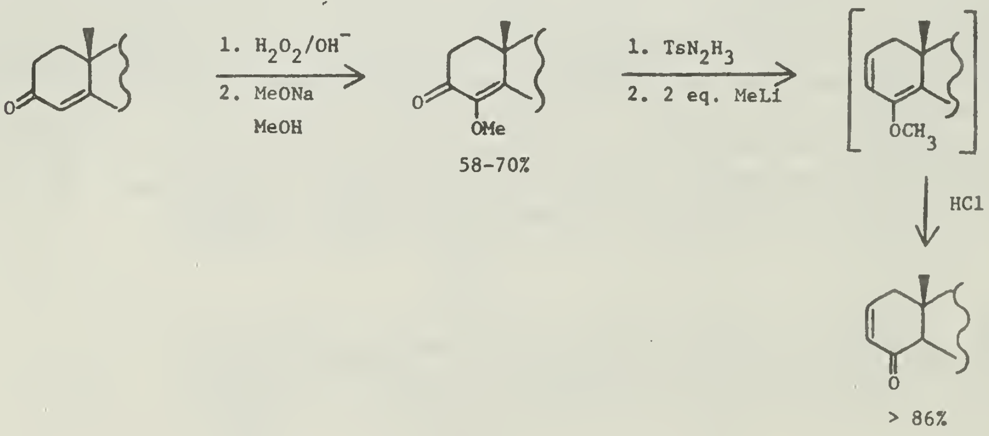
very sensitive to the size of the R group and to the conditions of the reaction.

Nakai[10c] has recently extended the tosylhydrazone sulfenylation to unsaturated systems. The method is limited because the sulfenylated product will aromatize to thioanisole derivatives when possible. (Eqn. 12)



(12)

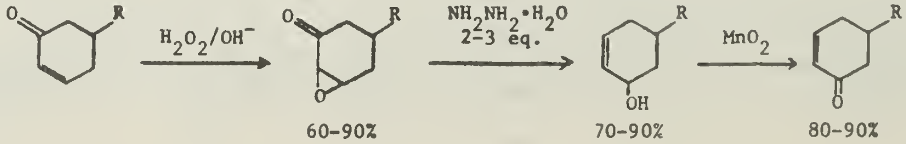
A novel carbonyl transposition was published by Reusch.[10d] (Eqn. 13) An unsaturated ketone is epoxidized with basic peroxide followed by base catalyzed opening of the epoxide and dehydration to yield an α methoxyenone. This enone is derivatized with tosylhydrazine and reacted with methyl lithium to undergo the Shapiro reaction. Quenching with hydrochloric acid reveals the transposed enone. Substituents in the α or α' position prohibit the epoxide opening.



(13)

1,3 Carbonyl Transpositions: Non-Alkylative.

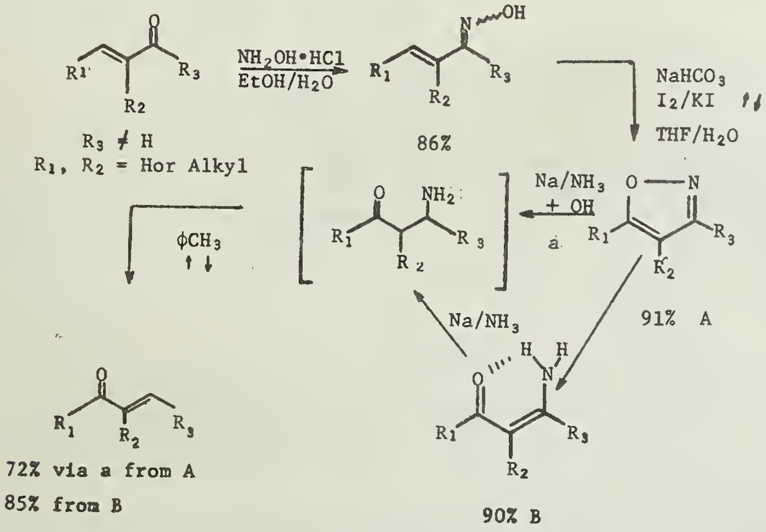
The Wharton Reaction. One of the most widely known carbonyl transpositions is based on the Wharton Reaction.[11a-d] Epoxidation of an unsaturated enone followed by hydrazine reduction yields a transposed allyl alcohol. Subsequent oxidation reveals the transposed enone. (Eqn. 14)



(14)

Enone-Oximes.

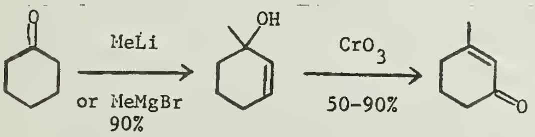
Büchi[12] investigated unsaturated oximes and found that they could be oxidized to isoxazoles with iodine in basic aqueous tetrahydrofuran. Isoxazoles can either be hydrogenated to vinylogous amides and further reduced to β-amino ketones with sodium in ammonia, or directly reduced to β-amino ketones with sodium in ammonia. The β-amino ketone is converted to the transposed ketone by either heating or acid catalyzed elimination (Eqn. 15).



(15)

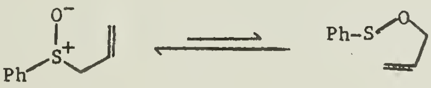
1,3 Carbonyl Transpositions: Alkylative

Oxidation of Tertiary Allylic Alcohols. Chromium based oxidation of tertiary allylic alcohols has been shown to yield unsaturated ketones with 1,3 transposed oxygen functionality.[13a-h] This reaction is complimentary to the Wharton reaction--an allylic alcohol is transposed to an enone instead of the reverse in a Wharton reaction. The tertiary alcohol is easily prepared by alkylating an unsaturated ketone with a Grignard reagent. Chromic acid or pyridinium chlorochromate have both been used as oxidants (Eqn. 16).



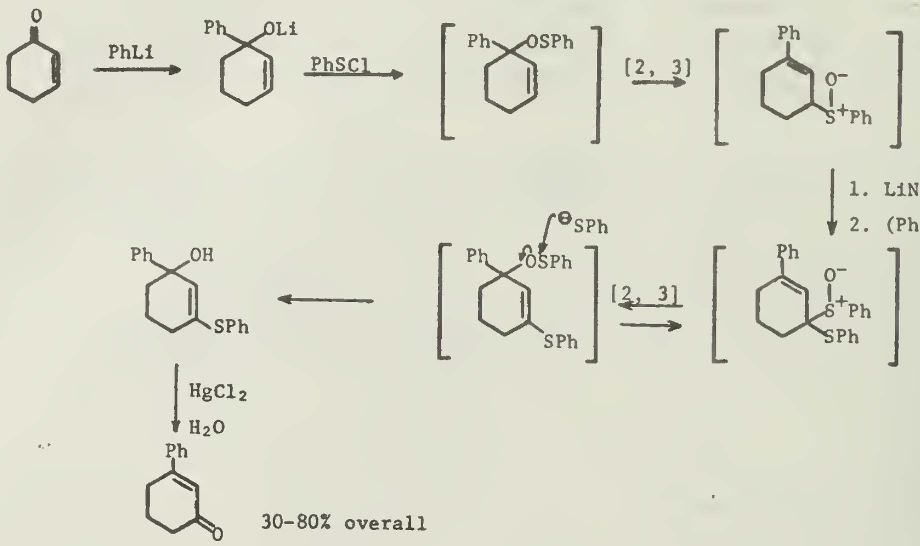
(16)

2,3 Sigmatropic Rearrangement. Mislow[14a,b] has studied allyl sulfoxides and shown that there is an equilibrium between allyl sulfoxide and allyl sulfenate (Eqn. 17). The equilibrium usually lies heavily toward the sulfoxide.



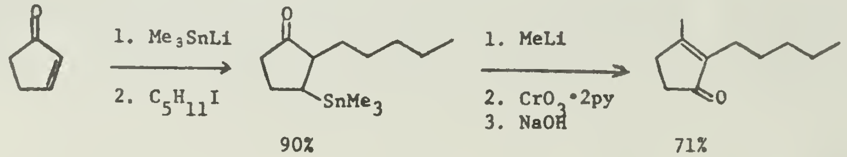
(17)

Trost[14c] used this knowledge to devise a novel carbonyl transposition. (Eqn. 18) An unsaturated ketone is treated with an organolithium reagent and the product is quenched with phenyl sulfenyl chloride. The resulting sulfenate undergoes a [2,3] sigmatropic rearrangement is situ to form an allylic sulfoxide. The sulfoxide is treated with lithium diethylamide at low temperature and added to diphenyl disulfide. The anion resulting from treatment with base is sulfenated and rearranges in situ to the sulfenate. The sulfenate undergoes desulfenylation with thiophenoxide to yield the hydroxy thioether. There is no net consumption of diphenyldisulfide in this process. Hydrolysis of the thioether in the presence of mercuric chloride yields the transposed ketone.



(18)

Stannylation. Still[15] has studied alkyl tin compounds and found that trialkyl stannyl anions add in a conjugate fashion to enones, yielding a specific enolate. The specific enolate may be alkylated with an electrophilic alkylating agent. The resulting ketone may then be alkylated with a nucleophilic alkylating agent. After dialkylation, oxidation of the alkylstannane yields the transposed enone. (Eqn. 19)



(19)

Summary. The carbonyl group plays a key role in organic chemistry. The ability to move it about a carbon skeleton greatly enhances the synthetic chemist's ability to construct molecules.

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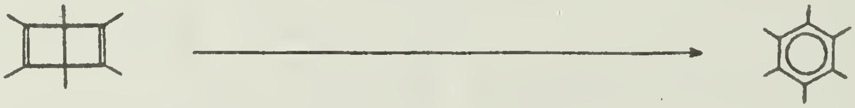
HEXAMETHYL(DEWAR BENZENE) ISOMERIZATION CATALYZED BY GROUND AND EXCITED STATE ELECTRON ACCEPTORS

Reported by Nancy Peacock April 15, 1982

Even though molecular isomerizations are common and a fundamental part of organic chemistry, their mechanisms are many times not well understood. Agents routinely employed to induce isomerizations are heat, light, or chemical catalysts. Our research was initiated in order to answer the following question: will generation of the radical cation of strained hydrocarbons facilitate their conversion to a more stable form? Because of molecualr orbital considerations, we chose to investigate the isomerization of hexamethyl(Dewar benzene) (HMDB) to hexamethlybenzene (HMB).

Figure I



We have found that several ground state electron acceptors (EA) will act to lower the energy of activation of HMDB isomerization. Tetracyanoquinodimethane (TCNQ) and three of its halogenated derivatives serve as excellent electron acceptors due to their high reduction potentials and lack of adverse reactivity. When an acetonitrile solution of HMDB and TCNQ is heated, isomerization does occur at a faster rate than when no electron acceptor is present. Furthermore, this rate appears to be directly related to the reduction potential of the electron acceptor, that is, the rate of isomerization increases with increasing reduction potential. At this point it has not been determined if an electron transfer has actually occurred or if HMDB is simply involved in a complex which acts to lower E_{act}.

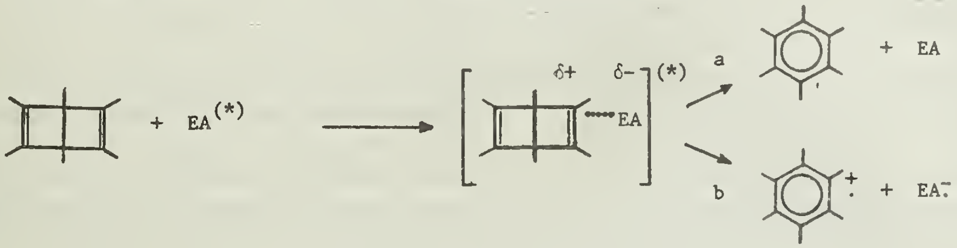
Excited state molecules generally make much better electron acceptors due to the half-filled low lying orbital. Others have investigated the use of electronically excited states to catalyze the isomerization of HMDB. In nonpolar solvents quantum yields of isomerization approach 1.0.[1,2] In polar solvents quantum yields exceed one and a radical chain mechanism has been proposed,[3] although until now no spectroscopic evidence has been presented for the existence of these radicals. Irradiation of charge transfer complexes involving HMDB and tetracyanobenzene or fumaronitrile has also been shown to catalyze HMDB isomerization.[4,5] Through the use of nanosecond laser spectroscopy, we have been able to investigate short-lived intermediates and determine to which extent HMDB$^{+\cdot}$ plays a part in these reactions.

Transient absorption spectra have been determined for both singlet and triplet excited state electron acceptors in the presence of HMDB. When an excited state singlet acceptor is used the yield of radical ions is dependent on the specific characteristics of each acceptor. In all spectra where radical ions are observed, no absorption can be assigned to HMDB$^{+\cdot}$. Only HMB$^{+\cdot}$ is seen. This fact is attributed to a very fast isomerization rate for the HMDB radical cation. Triplet excited state acceptors and HMDB give in all cases EA$^{-\cdot}$ and HMB$^{+\cdot}$.

Quantum yields for the excited state acceptors have been determined, but do not necessarily correlate to the yield of ions observed.

In summary, the isomerization of hexamethyl(Dewar benzene) to hexamethylbenzene is facilitated by ground state or excited state electron acceptors. The multiplicity of the intermediate complex strongly controls whether reaction occurs via path a or b. (Scheme I)

Scheme I



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$4_c + 3_c$ CYCLOADDITIONS: AN EFFICIENT APPROACH TO THE SYNTHESIS OF SEVEN-MEMBERED CARBOCYCLES

Reported by Brian D. Rogers April 19, 1982

The cycloaddition of allyl cations to conjugated dienes offers an efficient and general tool for the construction of seven-membered carbocycles. Until 1962, when Fort[1] obtained a seven-membered carbocycle from the base promoted addition of 1-chloro-1,3-diphenylpropanone to furan, these ring systems were most commonly synthesized by ring contraction or expansion.

Although allyl cations have been studied extensively,[2] their preparation was only accomplished in media which were unsuitable for cycloadditions. When solvolytic generation was used, the resulting allyl cation immediately reacted with the solvent. The reaction of the diene component with a highly acidic medium precluded the use of acidic media for cycloaddition reactions.

METHODS OF GENERATION

Silver Salt Method. In 1968, Hoffmann and co-workers[3] generated the 2-methylallyl cation in liquid sulfur dioxide from 2-methylallyl iodide and silver trichloroacetate or silver trifluoroacetate. Since that time numerous workers have used silver salts to generate allyl cations from the corresponding halides.[4,5,6,7,8,9,10,11]

In order to determine the geometry of the transition state for the silver ion induced cycloaddition, Hoffmann and Joy[3b] trapped the intermediate of the reaction between the 2-methylallyl cation and cyclopentadiene by performing the reaction in dichloromethane-acetonitrile. The nucleophilic acetonitrile attacks the cationic adduct to give exclusively the endo-substituted epimer. This result suggest an extended transition state for this system. Hoffmann also postulated that the 2-methylallyl cation is stabilized by a solvent separated ion-pair, in liquid sulfur dioxide, and the products result from the competition of the trichloroacetate counter-ion with the cyclopentadiene for the 2-methylallyl cation. Mann and Usmani[9] noted high stereoselectivity when silver tetrafluoroborate and triethylamine are used to generate oxyallyl species, but no stereoselectivity when triethylamine is used alone. Shimizu and co-workers[11] reported that the cycloaddition of the silver ion generated 2-(trimethylsiloxy)allyl cations to cyclopentadiene or furan, proceeds stereospecifically in nitromethane and nonstereospecifically in tetrahydrofuran-ether. Shimizu also showed that the stereo- and regiochemistry is dependent upon the solvent, the substrate, and the diene. A concerted mechanism was postulated in the nitromethane solvent system, and a stepwise mechanism in tetrahydrofuran-ether.

Reduction of α-Bromoketones.[12] In 1971, Noyori and co-workers[13] reduced 2,4-dibromo-2,4-dimethylpentan-3-one with $Fe_2(CO)_9$ in benzene, to produce the corresponding 2-oxyallyl cation. Since that time numerous workers have used $Fe_2(CO)_9$ to produce allyl cations from the corresponding haloketones.[14,15,17,18,19,20] A modification of this procedure was used by Monti and Harless in 1977,[16] whereby they generated cyclopentadieniron tricarbonyl, and reacted it with 1,1,3,3-tetrabromopropanone.

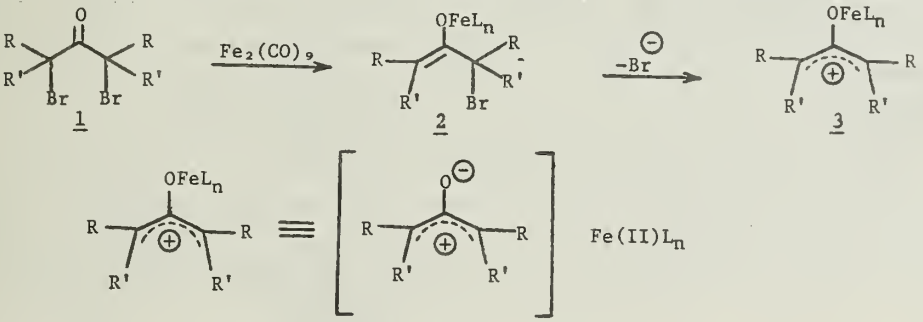
A zinc-copper couple has been used to reduce a variety of dihaloketones to yield the corresponding 2-oxyallyl cations.[21,22,23,24] The use of a zinc-silver couple has also been reported by Noyori.[25,26]

Yet another method for the reduction of bromoketones was developed in 1975 by Hoffmann and Iqbal,[27] which involved zinc dust and triethylborate in tetrahydrofuran. With this reagent, 3-bromo-1-iodo-3-methyl-2-butanone was reduced to the corresponding 2-oxyallyl cation. Other examples of this method were reported in 1981 by Mann and co-workers,[28] and Ansell and co-workers.[29]

The electrochemical reduction of α,α'-dibromoketones was reported by Fry and O'Dea in 1975[30] using a mercury cathode in an acetic acid solvent system.[31] Fry and Herr,[32] also reported a similar reduction using ultrasonically dispersed mercury in acetic acid.[33]

The reduction of 1,3-dibromo-1,3-diphenylpropanone by sodium iodide in both acetonitrile and acetone, was reported in 1967 by Cookson and co-workers,[34] and in 1974, Hoffmann and co-workers[35] reported the reduction of α,α'-dibromoketones by sodium iodide in the presence of copper in acetonitrile. Cowling and Mann[36] reported the reduction of various alkyl-substituted α,α'-dibromoketones with sodium iodide in the presence of copper, and in 1979, Kato and co-workers[37] reported the reduction of 2,4-dibromo-3-propanone by potassium iodide in the presence of copper metal in acetonitrile.[38]

The mechanism of formation of a 2-oxyallyl cation by reductive dehalogenation of bromoketones, was shown to be dependent upon the reducing agent used to generate the cation. In the case of reduction via $Fe_2(CO)_9$, the mechanism by which the 2-oxyallyl cation is formed was postulated to be as shown in Figure 1 by Noyori and co-workers in 1978.[20h] Initially, the iron enolate 2 is formed by either two-electron reduction of the dibromoketone 1 with an iron carbonyl, or oxidative addition of the carbon-bromine bond of 1 onto the zerovalent iron atom,[39] followed by carbon to oxygen migration to the more stable structure 2.



L = Br, CO, solvent, etc.

Figure 1. Formation of a 2-Oxyallyl Cation by Reaction with $Fe_2(CO)_9$.

The second step is an S_N1-type or ferrous ion assisted elimination of the allylic bromine atom to produce the reactive oxyallyl species 3. When the reductive dehalogenation is accomplished by a zinc-copper couple, a mechanism similar to that proposed for the reductive dehalogenation by $Fe_2(CO)_9$ was postulated by Hoffmann[12b] to occur as shown in Figure 2.

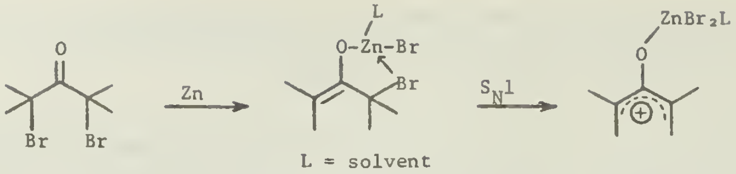


Figure 2. Formation of a 2-Oxyallyl Cation by Zn/Cu Couple.

In 1979, Hoffmann and co-workers[38c] postulated the mechanism shown in Figure 3, for the reductive dehalogenation of α,α'-dibromoketones by alkali-metal iodides in the presence of copper. Three nucleophilic substitutions by iodide ion produce the allylic iodide 4, which undergoes a S_N1-like fragmentation to produce the 2-oxyallyl cation 5. A mechanism for both the electrochemical and dispersed-mercury reduction was postulated in 1979 by Fry and Ginsburg[31a] and is shown in Figure 4.

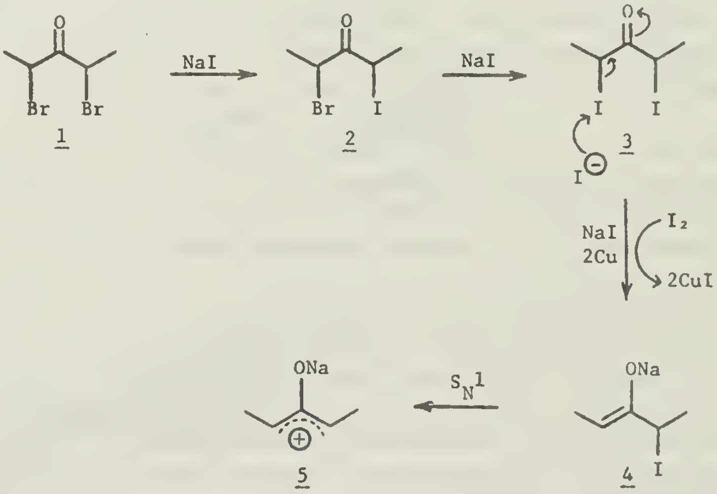


Figure 3. Formation of a 2-Oxallyl Cation by NaI/Cu.

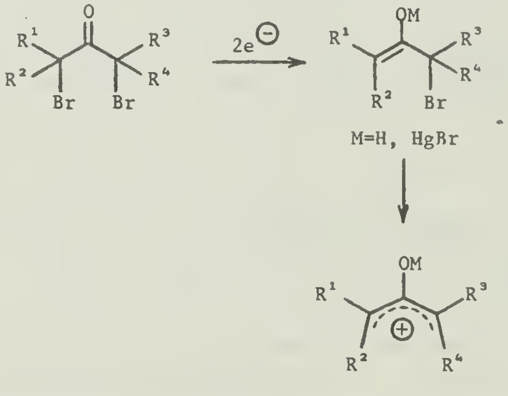


Figure 4. Formation of a 2-Oxyallyl Cation by Either an Electrochemical Reduction or Dispersed Mercury.

A possible mechanism for the triethylborate-zinc reduction of α,α'-dibromoketones was postulated in 1975 by Hoffmann and Iqbal.[27] The mechanism, as shown in Figure 5, begins with enolization by the loss of a proton rather than the reductive removal of bromine. The boron enolate 3 can ionize, with intramolecular nucleophilic assistance by oxygen, to the allyl cation 4. Consistently, ketones with no protons on the carbon α to the carbonyl do not react.

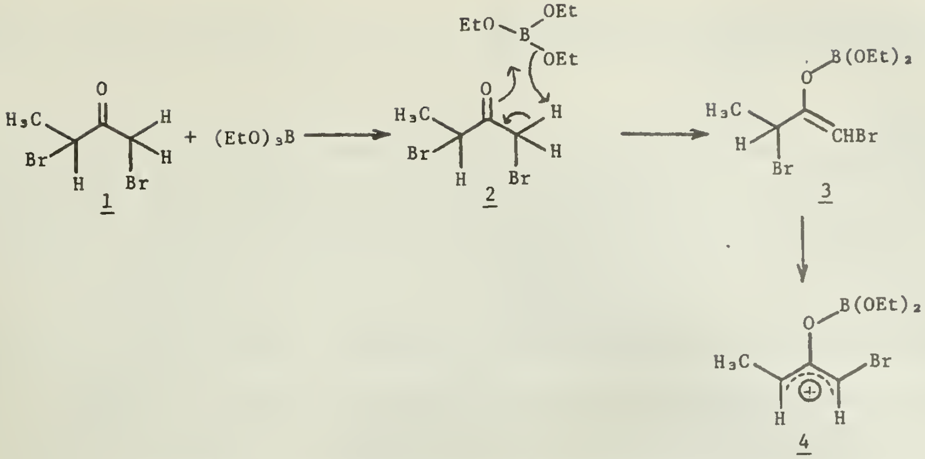


Figure 5. Formation of a 2-Oxyallyl Cation by $(EtO)_3B/Zn$.

These oxyallyl cations have multifaceted reactivities which are a function of solvent,[26a] the degree of ionic character in the oxygen-metal bond, and the degree of stabilization afforded by the substituents on the α-carbons. In general, the reaction of these oxyallyl cations with reactive dienes such as furans, appears to proceed in a concerted fashion and affords 4_c+3_c cycloaddition products. Less reactive dienes such as pyrroles, or dienes which are conformationally mobile,[23] may react by way of a two-step mechanism.[36]

Acidic Two Phase Dehydration of Allylic Alcohols. In 1980 and 1981, Hoffmann and Vathke-Ernst dehydrated 2,4-dimethyl-3-penten-2-ol,[40] 4-methyl-3-penten-2-ol,[41] and 2,3-dimethyl-3-penten-2-ol[42] in an aqueous acid (p-toluenesulfonic acid)-pentane two phase system and generated the corresponding allyl cations.

The cations generated from 2,4-dimethyl-3-penten-2-ol, and 4-methyl-3-penten-2-ol possessed no propensity to undergo 4_c+3_c cycloadditions with cyclopentadiene. This was postulated, by Hoffmann, to be due to the lack of a stabilizing moiety on the central carbon of the allyl system. This carbon must bear a positive charge upon reacting in a 4_c+3_c manner, as is shown in Figure 6, and the lack of a substituent which is able to stabilize this charge, probably prevents this reaction pathway from being energetically favorable. Instead, these unstabilized allyl cations undergo electrophilic addition to cyclopentadiene, and Diels-Alder-like addition to cyclopentadiene which is postulated by Hoffmann[40c] as being a step-wise reaction, mechanistically related to the $AlCl_3$ catalyzed addition of 4-methylpent-3-ene-2-one to cyclopentadiene.

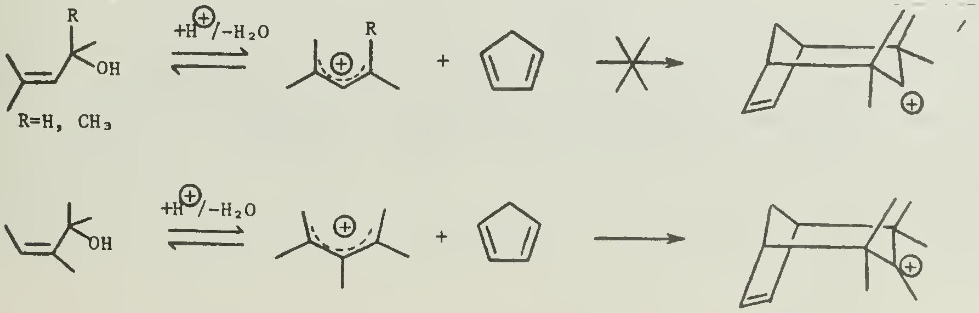


Figure 6. $4_c + 3_c$ Cycloadditions of Allyl Cations to Cyclopentadiene.

Miscellaneous Generation Methods. In 1972, Hoffmann and co-workers[43] generated allyl cations from 2-dimethylamino-4-methylene-1,3-dioxolanes in furan.

In 1980, Hoffmann and Matthei[44] generated 2-oxyallyl cations by first, trifluoroacetylation of various allylic alcohols, and then heterolysis of the resulting ester with either $ZnCl_2$ or $ZnBr_2$ in the presence of ethyldiisopropylamine in either acetonitrile or methylene chloride solvent systems.

In 1979, Hosomi and co-workers[45] generated a 2-oxyallyl cation by heterolysis of 3-bromo-3-methyl-2-trimethylsiloxy-1-butene with $ZnCl_2$ in methylene chloride.

In 1979, Matzinger and Eugster[46] reported the generation of a 2-oxyallyl cation by treatment of 2-chlorocyclohexanone with sodium hydride.

Representative Recent Synthetic Applications. In 1979, Noyori and co-workers[19] reported the intramolecular cyclization shown in Figure 7. This cyclization permits the direct synthesis of an oxidoperhydroazulene structure that is the basic skeleton of daucon, ambrosic acid, and geracrol among others.

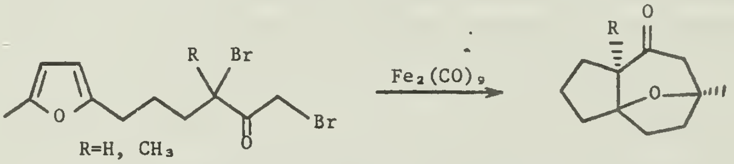


Figure 7. Synthesis of Oxidoperhydroazulene Structure.

In 1979, Wierenga and co-workers[20t] reported the synthesis of ionophores, as shown in Figure 8, utilizing the $Fe_2(CO)_9$-promoted addition of 1,1,3,3-tetrabromopropanone to cyclopentadiene.

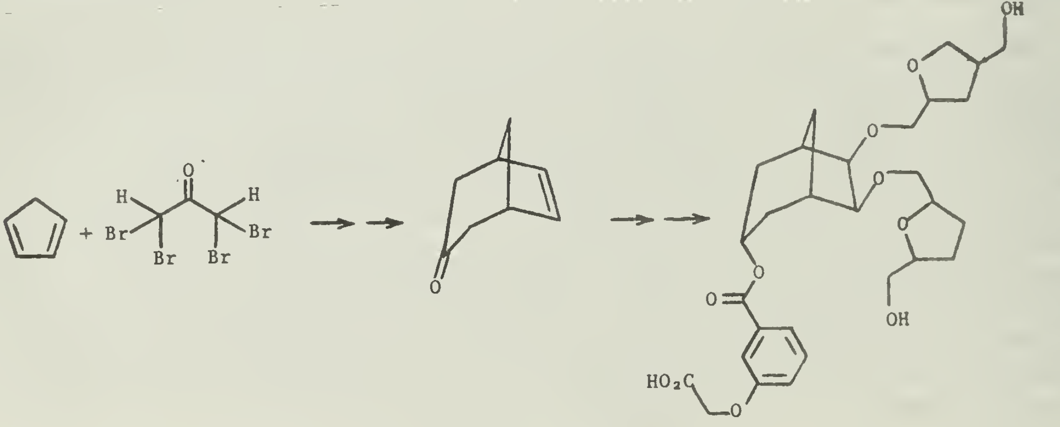


Figure 8. Synthesis of Ionophores.

In 1980, Noyori and co-workers[20u] reported the synthesis of 4-phenylated pyrimidine nucleosides utilizing the $Fe_2(CO)_9$ promoted reductive coupling of 1,1,3,3-tetrabromopropanone and 2-phenylfuran, as shown in Figure 9. These 4-phenylated pyrimidine nucleosides are unaccessible by any other known procedure.

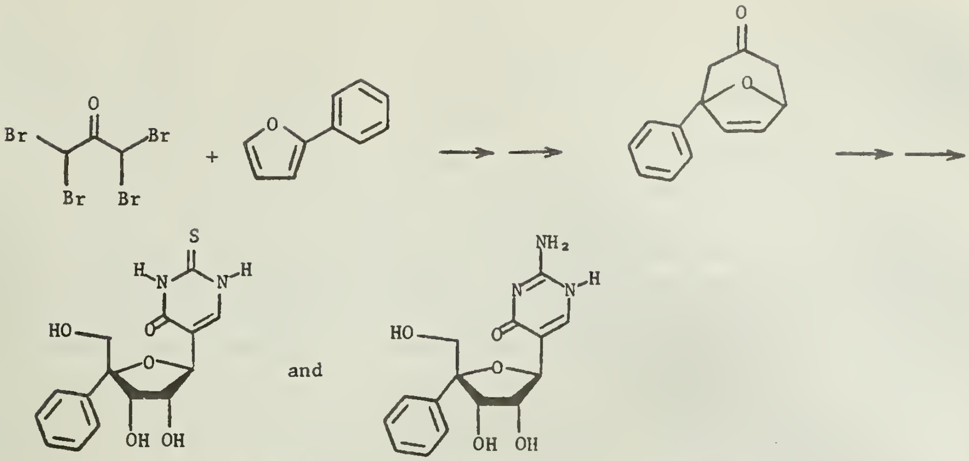


Figure 9. Preparation of 4-Phenylated Pyrimidine Nucleosides.

In 1981, Ansell and co-workers[29] reported the synthesis of a thromboxane A_1 analogue, (±)-9a-homo-(11,12)-deoxa-(11,12)-methylene thromoboxane A_1, utilizing the triethylborate-zinc promoted cycloaddition of 1,1,3,3-tetrabromopropanone to furan as shown in Figure 10.

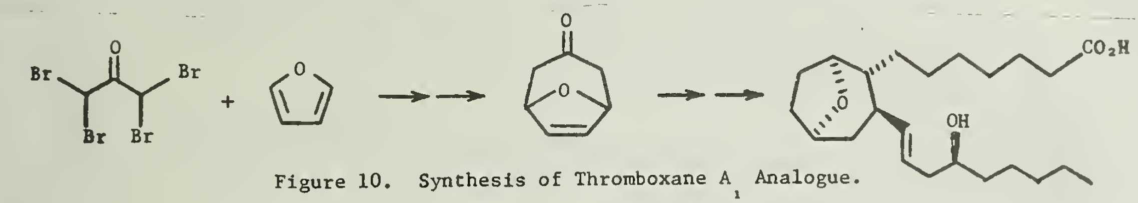


Figure 10. Synthesis of Thromboxane A_1 Analogue.

In 1981, Cowling and co-workers[28] reported the synthesis of a muscarine analogue 1 and of α-multistriatin analogues 2, as shown in Figure 11. The triethylborate-zinc promoted cycloaddition of 1,1,3,3-tetrabromopropanone with furan utilized to produce the muscarine analogues, and the silver tetrafluoroborate-triethylamine promoted cyclization of 2-bromopentan-3-one with the appropriately substituted furan was utilized to produce the α-multistriatin analogues.

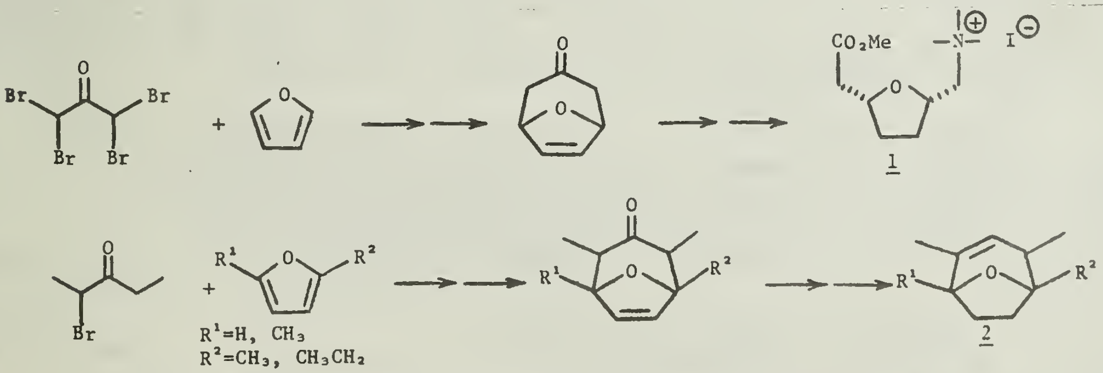


Figure 11. Preparation of Muscarine and Multistriatin Analogues.

In 1976, White and co-workers[22] reported the synthesis of (±)-nonactic acid, utilizing the zinc-copper promoted cycloaddition of 2,4-dibromo-3-pentanone to furan as shown in Figure 12.

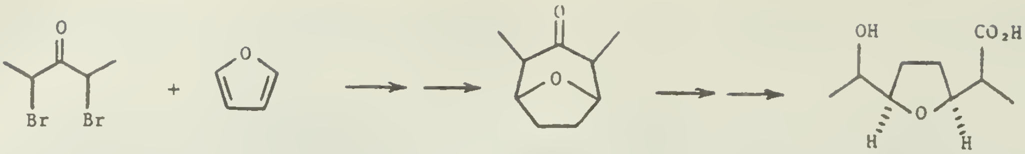


Figure 12. Synthesis of (±) Nonactic Acid.

In conclusion, the scope of the 4_c+3_c cycloaddition is just now beginning to be explored. The stereospecificity, under reaction conditions which promote a concerted-like mechanism, and the overall reduction in the number of steps, are definite advantages over other methods for creating seven-membered carbocycles.

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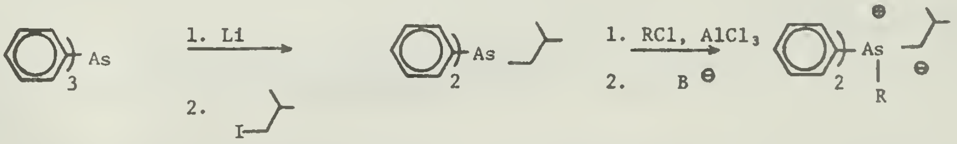
ARSONIUM YLIDES

Reported by Scott Culley April 22, 1982

Synthetic chemists are currently exploring arsonium ylides as a tool to both complement and supplement traditional phosphorus and sulfur ylides. Arsonium ylides can effect cyclopropanations, epoxidations, and olefinations. They often react where phosphorus ylides fail to react, and frequently provide higher stereoselectivity than sulfonium ylides.

Arsonium ylides are analoges of phosphorus ylides or Wittig reagents. Stabilized arsonium ylides (β-Keto, β,β-biphenylene, or β-cyano) can be prepared and isolated by treatment of triphenylarsine with an α-haloketo compound, α halofluorene, or halonitrile followed by deprotonation with alkoxide or organolithium bases.[1-4] Semistabilized (benzylic) ylides are generated in the same manner and used *in situ*.[5-17] Triphenyl arsonium methylide or ethylide can be prepared by the reaction of the appropriate trialkyloxonium fluoroborate with triphenylarsine followed by deprotonation.[8] Longer chain ylides have been generated by treating an alkyl triflate with triphenylarsine followed by deprotonation.[19] For cases where direct alkylation of triphenylarsine is not possible, Still has developed a procedure which employs lithium diphenylarsenic as a superior nucleophile (Scheme 1).[19]

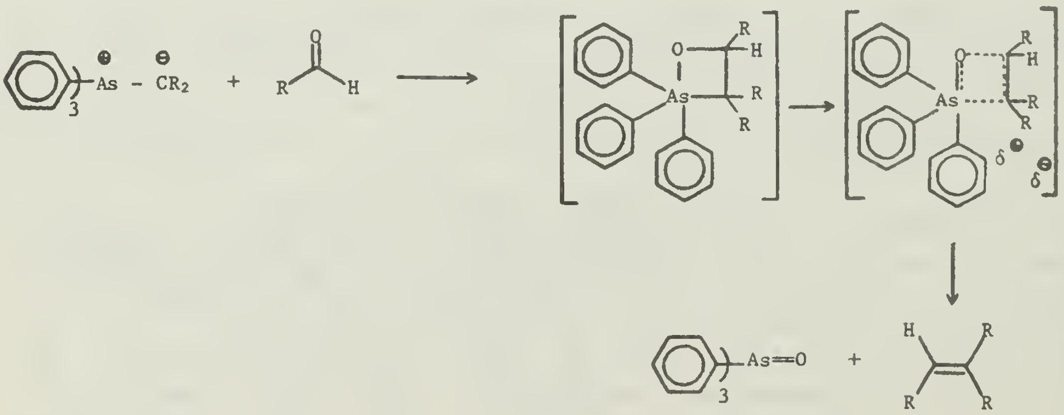
Scheme 1



(1)

Arsonium ylides undergo a variety of reactions. Stabilized ylides react with aldehydes and ketones to yield trans olefins, while unstabilized ylides give the trans epoxides.[1,4-6,10,11,13-17,19] The mechanism which has been proposed involves formation of an arsonium betaine followed by cyclization to form a pentacoordinate arsorane. The arsorane then decomposes to yield either arsine oxide and olefin or arsine and epoxide. Trippet has proposed that the α carbon bears a fractional negaive charge in the transition state and that substituents which stabilize this charge lead to faster olefin formation (Scheme 2).[5]

Scheme 2



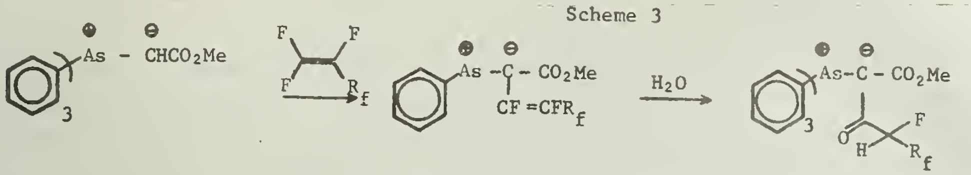
(2)

Still has employed unstabilized arsonium ylides to epoxidize aldehydes and ketones with high stereoselectivity.[19]

Triphenylarsonium carbomethoxymethylide and benzoylmethylide react with α,β-unsaturated esters and ketones to yield cyclopropanes or normal Wittig products.[3] These arsonium ylides react to yield cyclopropanes if the ketone is phenyl substituted while olefins are obtained if the ketone is methyl substituted. Huang has employed these ylides in the stereospecific synthesis of 1,2,3-trisubstituted cyclopropanes.

Huang has also found that arsonium ylides are more reactive than phosporus ylides with fluoroalkenes.[2] They have isolated both trans olefins and carbonyl compounds from the reaction of triphenylarsine carbomethoxymeth ylide with fluorinated olefins (Scheme 3).

Scheme 3



(3)

Synthetic work employing arsonium ylides while receiving less attention than traditional ylides has now been expanded to take advantage of the unique properties of arsenic. New work will almost assuredly continue in this field, and should provide the synthetic chemist with powerful additions to his battery of synthetic transformations.

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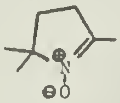
PREPARATION AND CYCLOADDITION REACTIONS OF ENDOCYCLIC NITRONES

Reported by Steve Ashburn May 3, 1982

Compounds containing an imine N-oxide functional group are known as nitrones and have found considerable synthetic utility when contained within five- and six-membered rings as shown in structures 1, 2, and 3.[1] Nitrones in this class have been prepared by intramolecular condensation of a hydroxylamine and a carbonyl group,[2-5] by air oxidation of hydroxylamines,[2,6] by potassium ferricyanide[7] and mercuric oxide[8,9] oxidation of hydroxylamines, by silica gel catalyzed rearrangement of an oxaziridine,[10] by peracid oxidation of an isoxazolidine,[11] and by a retro [2+3] cycloreversion reaction of an isoxazolidine.[11] They are also reactive toward dipolariphiles, forming adducts with cyclohexene,[12] norbornene,[13] phenyl isocyanate,[6] cyclohexenone[14] and many other activated olefins.[5,14,15] Nitrone cycloaddition reactions are key steps in the synthesis of members of the tropane,[11] pyrrolizidine[9,16] and elaeocarpus[17] alkaloid families,[19] as illustrated by Tufariello's cocaine (4) synthesis,[11,18] below.



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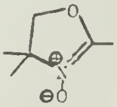

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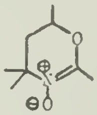

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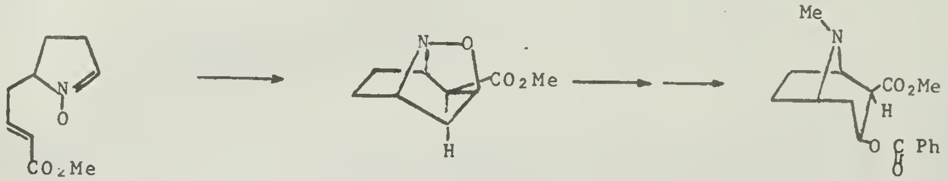

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Recently Keana has described the preparation of a new type of cyclic nitrone, an α-alkoxy nitrone, having oxazoline N-oxide and dihydrooxazine N-oxide structures (e.g. 2 and 3).[10] These also undergo cycloaddition reactions with dipolariphiles.

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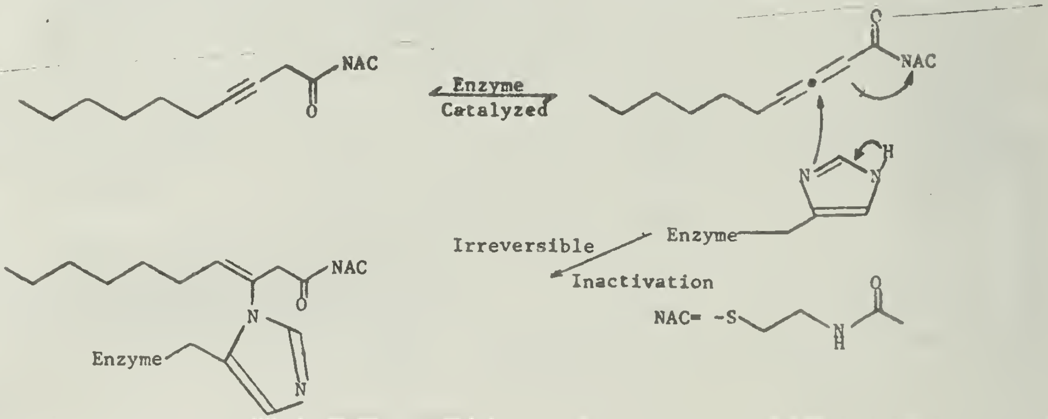
RECENT ADVANCES IN THE DESIGN OF SUICIDE ENZYME INACTIVATORS

Reported by Scott Daniels May 10, 1982

Reagents which can covalently bind to the active site of an enzyme have seen increasing use in recent years. These agents are useful in delineating the environment of the active site, as well as in determining the mechanisms of enzyme catalysis. Many of these compounds have also shown promise in studying the physiological importance of enzymatic pathways and in the treatment of disease.[1]

Inhibitors that contain a latent reactive moiety which is revealed after catalytic action by the enzyme followed by covalent attachment at the active site are called k_{cat} inhibitors or suicide enzyme inactivators. The model for this type of suicide inhibition was provided by the research of K. Bloch on the inhibition of β-hydroxydecanoyl thioester dehydrase by $\Delta^{(3,4)}$-decynoyl-N-acetyl cysteamine.[2] This enzyme normally catalyzes the reversible interconversion of hydroxydecanoyl thioesters with their α,β-trans and β,γ-cis counterparts. $\Delta^{(3,4)}$-Decanoyl-N-acetyl cysteamine, however, was found to irreversibly inactivate the enzyme via enzyme catalyzed allene formation and subsequent alkylation by a histadine residue in the active site.[3]



Numerous suicide enzyme inactivators have been developed since the work of Bloch, many of which are outlined in several reviews. The majority of these compounds are amines or amino acids containing suitably positioned acetylenic or vinylic groups. Catalytic action by the enzyme reveals a Michael acceptor which then traps any proximal nucleophile in the enzyme active site.

More recent examples of enzyme inactivation by suicide substrates have also utilized Michael acceptors as the inactivating species. These include the irreversible inactivation of amino acid decarboxylases by α-halomethyl amino acids[4], of ketosteroid isomerase by an acetylenic secosteroid[5], of alanine racemace by β-haloalanines[6] and o-carbamoylserine[6], of GABA transaminase by vinyl GABA[7] and 4-amino-crotonic acid[8] derivatives, of ribonucleotide reductase by 2'-deoxyfluoroadenosine-5'-diphosphate[9], and of thymideilate synthetase by nitro[10] and derivatives of 2'-deoxyuridilate.

Other suicide enzyme inactivators have recently been developed which have novel mechanisms for enzyme inactivation. Aromatase is inactivated by an unsaturated epoxide or allene oxide generated by the catalytic action of the enzyme on a propargylic alcohol of nortestosterone.[11] 2-Amino-4-chloro-5-(p-nitrophenylsulfinyl) pentanoic acid inactivates cystathionine-γ-synthetase and methionine-γ-lysase.[12] Enzymatic hydrogen abstraction leads to a β-carbanion-assisted γ-elimination which produces an allyl sulfoxide-enzyme-pyridoxal adduct. This undergoes a spontaneous 2,3-sigmatropic rearrangement to an electrophilic allyl sulfenate ester which is thought to be the inactivating species.[12] Alcohol dehydrogenase is inactivated by the natural product, coprine.[13] After enzymatic hydrolysis and dehydration, coprine yields cyclopropanone which then forms a kinetically stable thiohemiketal with the active site thiol. Clavulanic acid[14] and penicillanic sulfones[15] are thought to inactivate β-lactamases through the formation of an acyl enzyme which is stabilzied to hydrolysis by the presence of an α,β-unsaturation.

The development of these suicide enzyme inactivators for specific enzymes provides a handle for modulating enzymatic activity. This type of control is not only invaluable in studying enzymatic processes but should prove to be useful in clinical applications.

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